Targeting CD38 to optimize PD-(L)1 and CTLA-4 immune checkpoint blockade

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
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Disclosures

- Grant/Research Funding: AstraZeneca, Janssen Research & Development, Takeda.
- Advisory Board/Consulting: AstraZeneca, Janssen R&D, Sanofi, Ribon Therapeutics, Mitobridge, Alethia Biotherapeutics.

- I will discuss investigational uses of immunotherapy drugs.

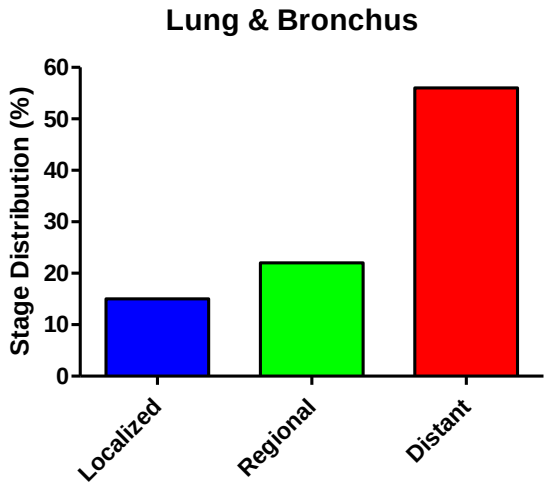
Outline

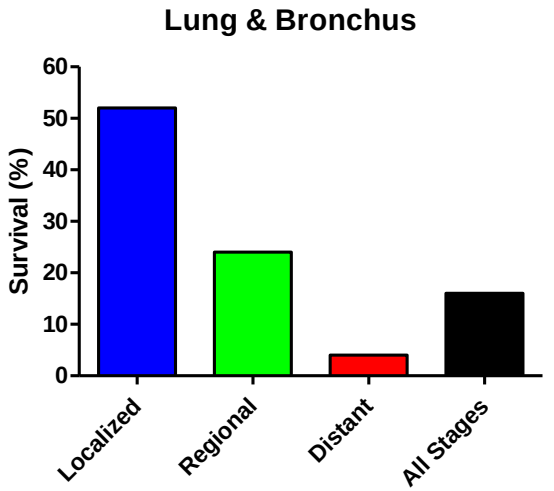
- Challenge of immunotherapy in NSCLC
- Pre-clinical modeling of immune checkpoint therapy resistance
- Roles for CD38 in the immune microenvironment
- Translational biomarker development in NSCLC

Lung cancer accounts for a significant percentage of cancer-related disease burden and mortality

Estimated Deaths

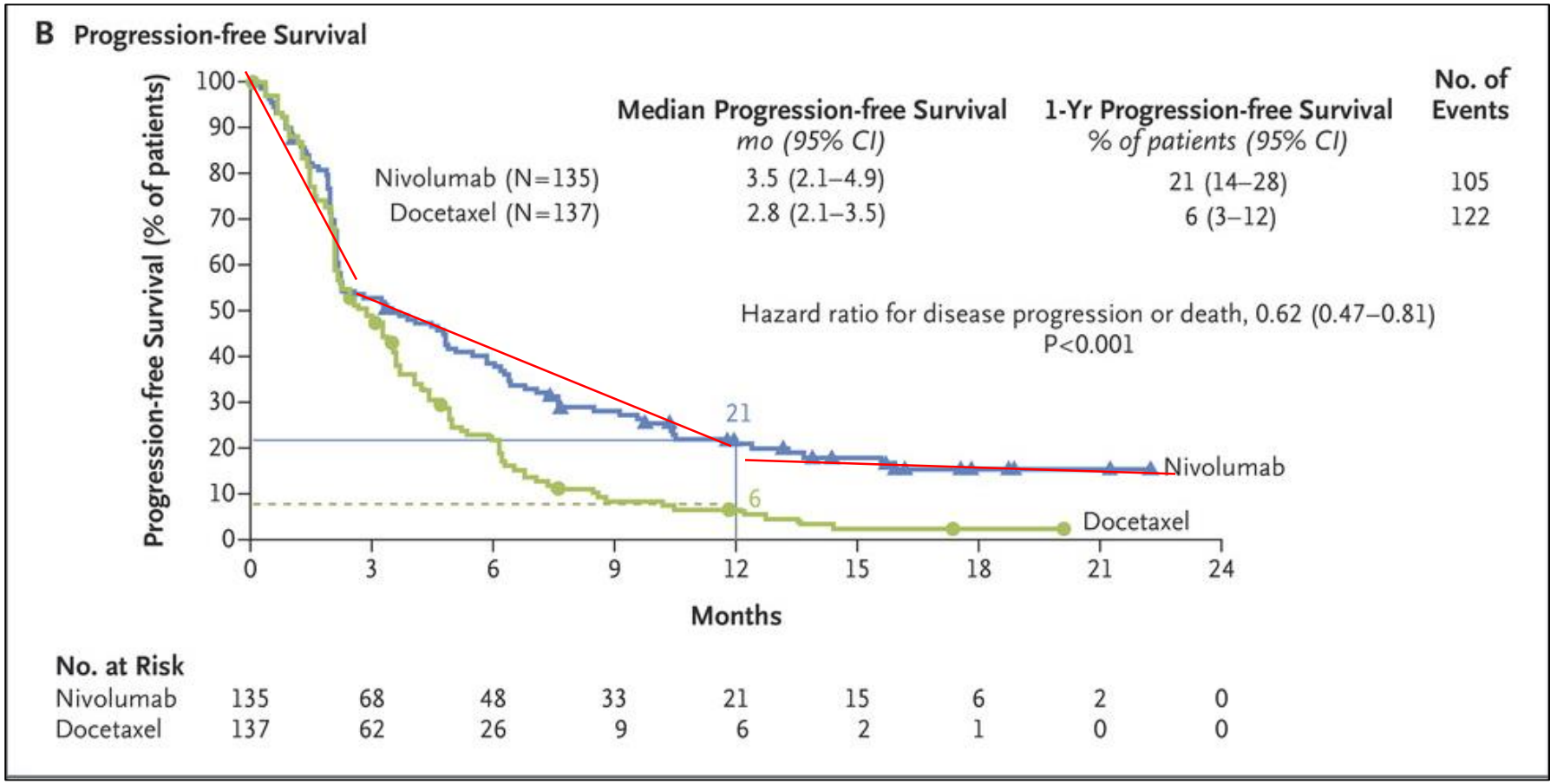
Males			Females		
Lung & bronchus	76,650	24%	Lung & bronchus	66,020	23%
Prostate	31,620	10%	Breast	41,760	15%
Colon & rectum	27,640	9%	Colon & rectum	23,380	8%
Pancreas	23,800	7%	Pancreas	21,950	8%
Liver & intrahepatic bile duct	21,600	7%	Ovary	13,980	5%
Leukemia	13,150	4%	Uterine corpus	12,160	4%
Esophagus	13,020	4%	Liver & intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%	Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%	Brain & other nervous system	7,850	3%
All Sites	**321,670**	**100%**	**All Sites**	**285,210**	**100%**





Siegel et al, 2019

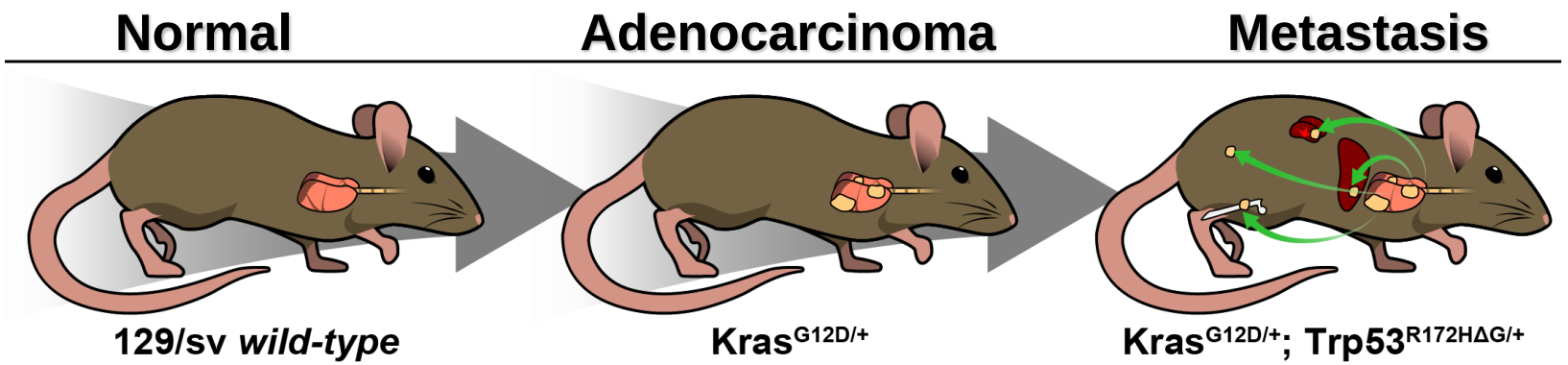
Efficacy of anti-PD-1 Immunotherapy vs Chemotherapy in Patients with Advanced NSCLC

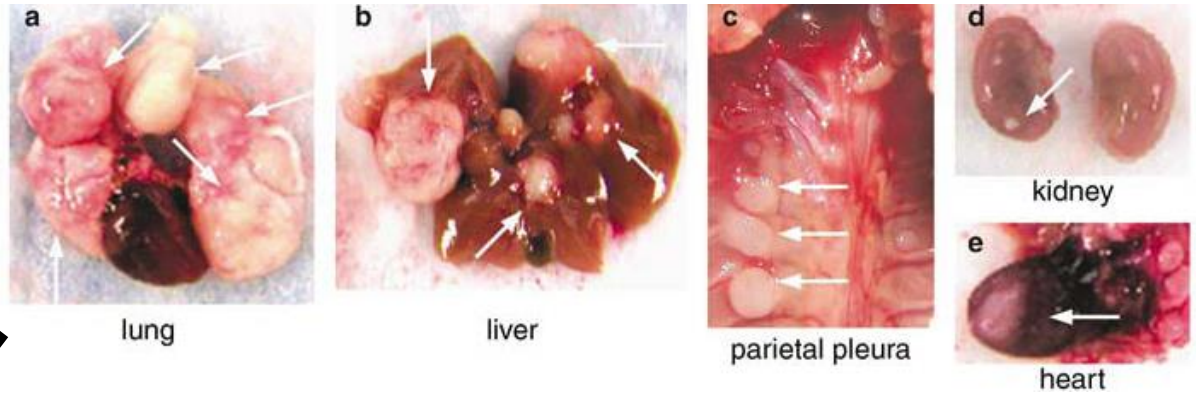


Brahmer J et al. *N Engl J Med* 2015;373:123-135.

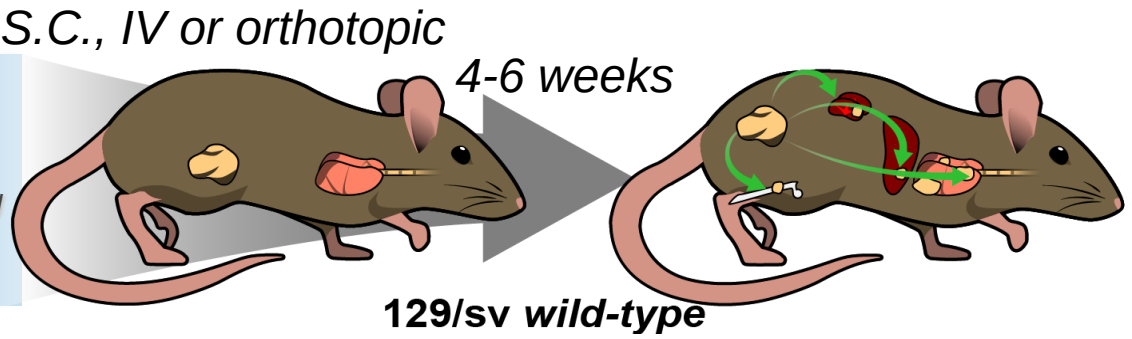
Modeling immune checkpoint therapy resistance & CD38

GEMM & Syngeneic Models to Study Lung Cancer





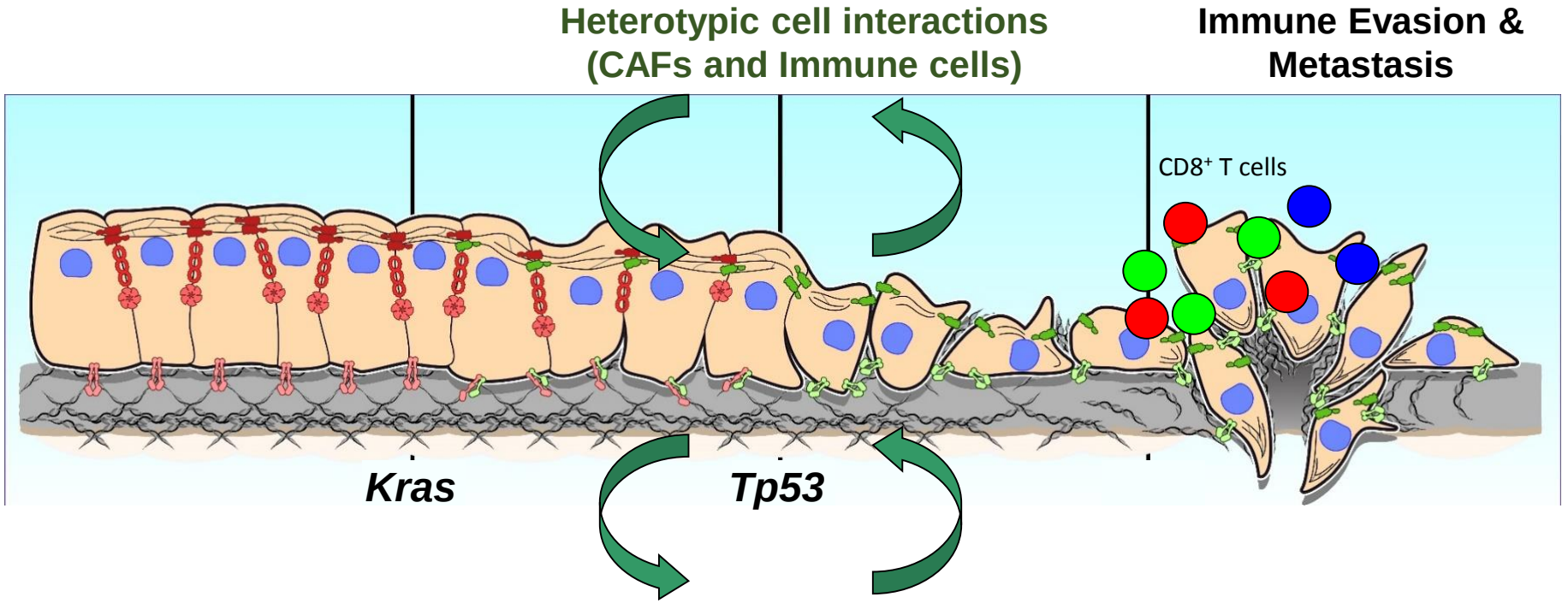
Lung cancer cell lines derived from *Kras*^{G12D};*Trp53*$^{R172H\Delta g}$ mice (KP cell lines)



Phenotypes
- Highly metastatic (344SQ)
- Modestly metastatic
- Non-metastatic (393P)

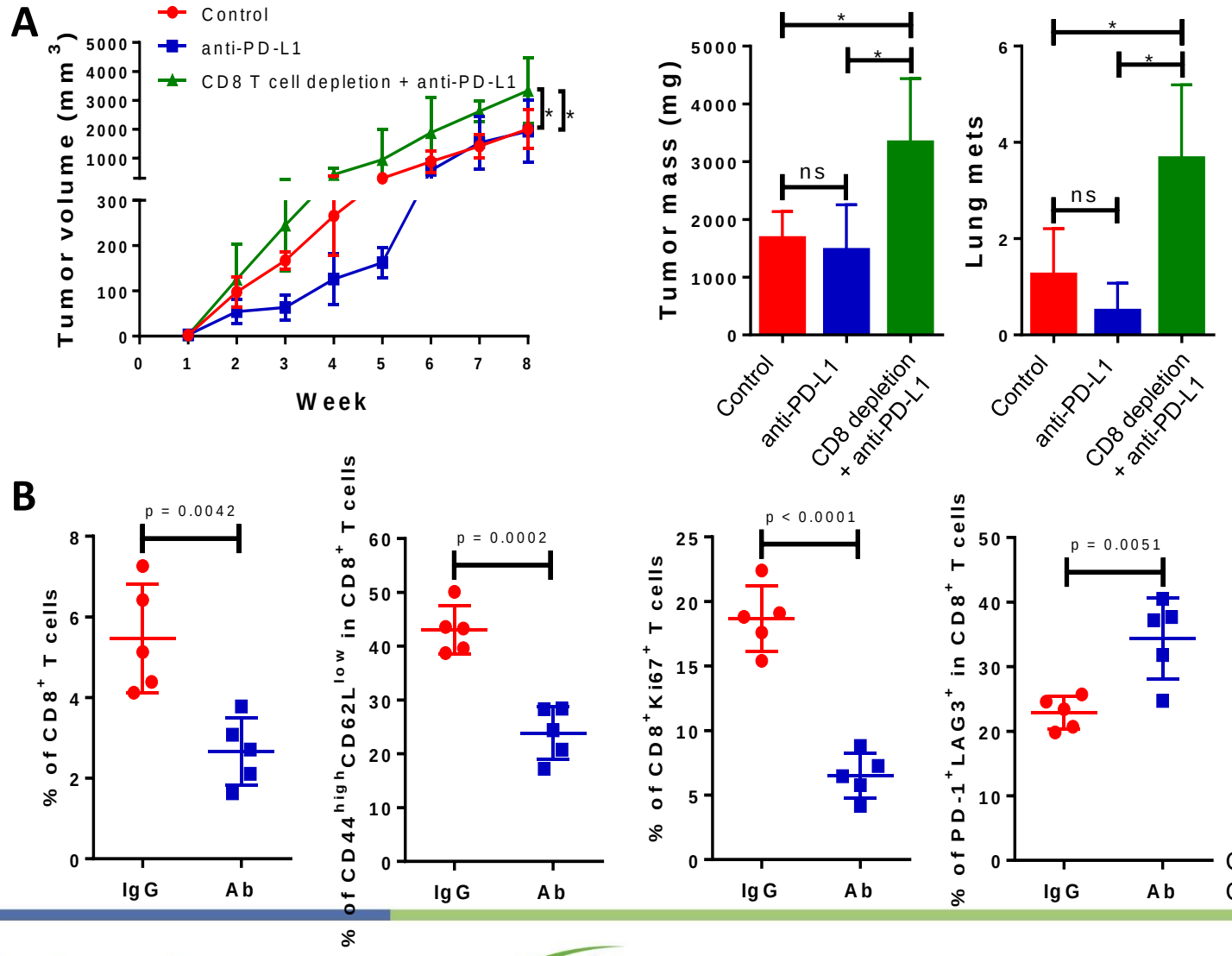
Zheng et al., *Oncogene*. 2007; Gibbons et al, *Genes & Dev.*, 2009.

Tumor-microenvironment interactions during progression & metastasis



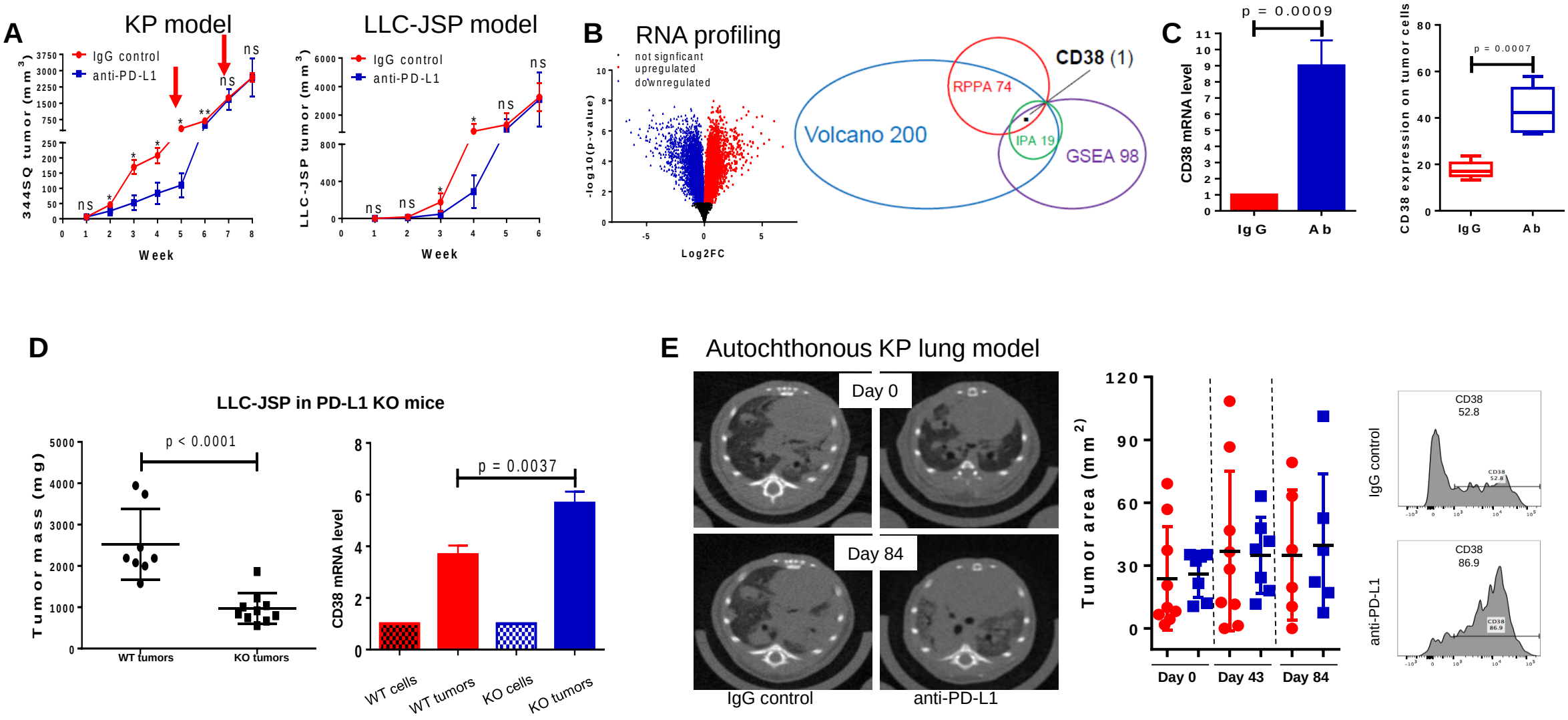
Gibbons et al, *Genes & Dev.*, 2009
Yang et al, *JCI*, 2011
Ahn et al, *JCI*, 2013
Kundu et al, *Nature Communications*, *2018*
Grzeskowiak et al, *Nature Communications, 2018*
Peng et al, *Science Translational Medicine*, 2019

CD8 T cell response controls tumor growth and metastasis, but efficacy of anti-PD-(L)1 is lost over time



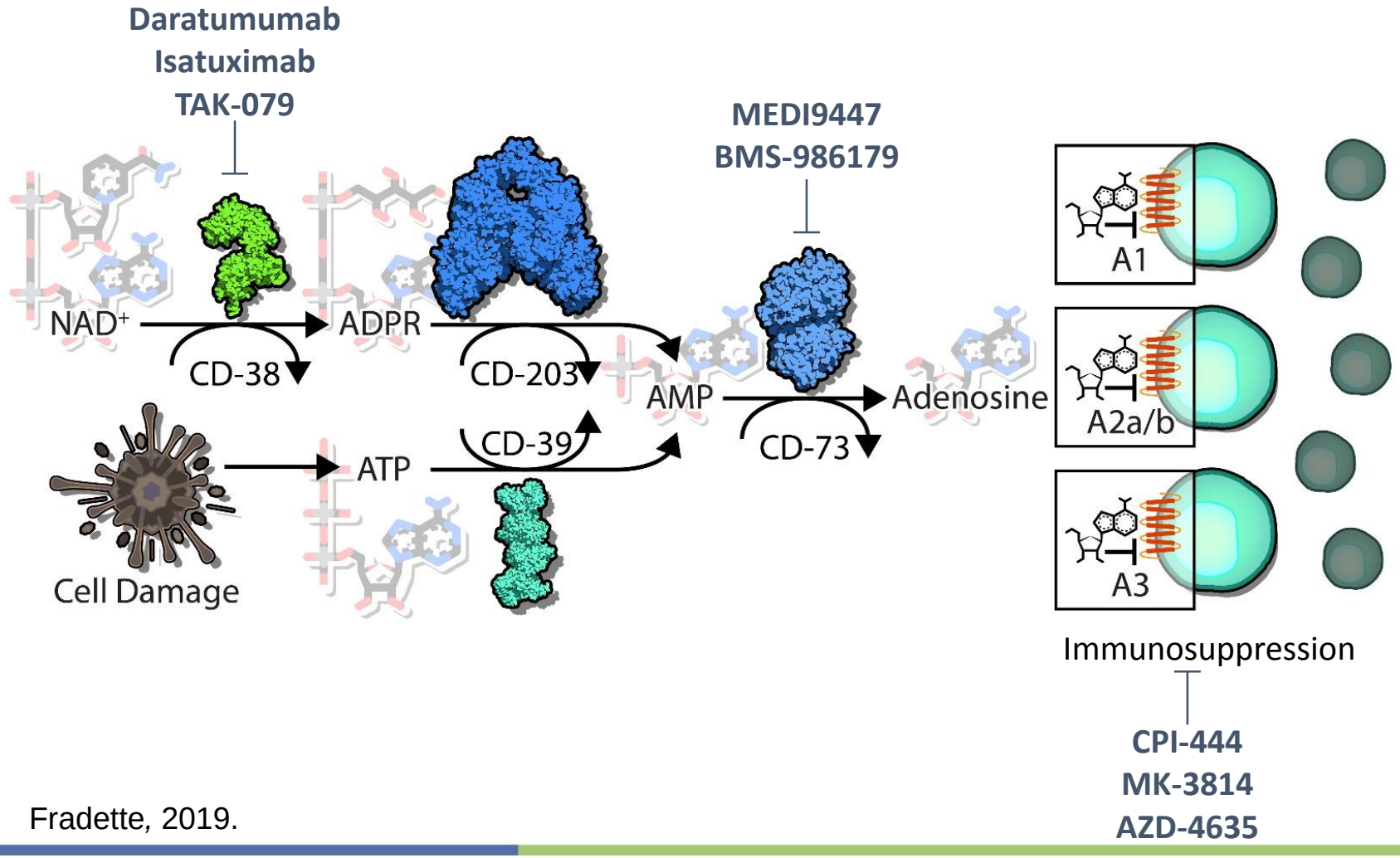
Chen et al, *Nature Communications*, 2014.
Chen et al, *Cancer Discovery*, 2018.

Identification of CD38 in pharmacologic & genetic models of *in vivo* anti-PD-L1/PD-1 resistance



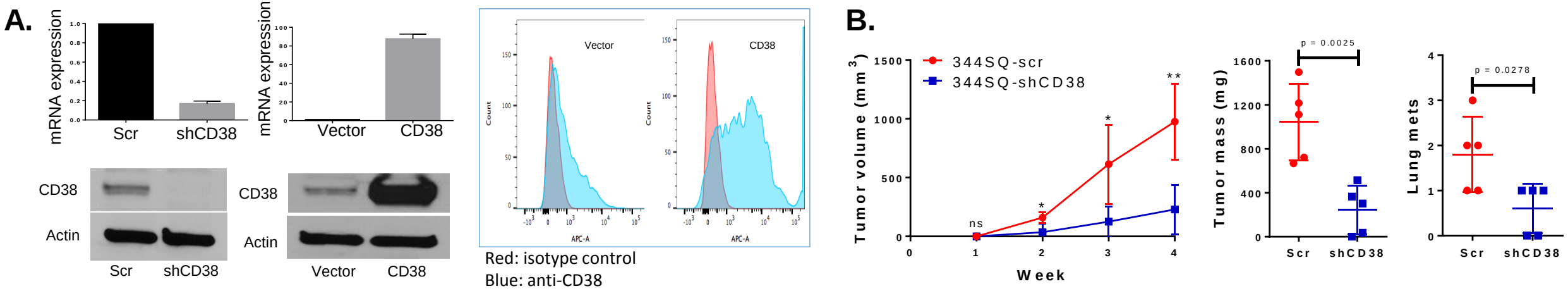
Chen et al, *Cancer Discovery,* 2018.

CD38: an NAD hydrolase/cyclase that provides an alternate pathway for extracellular adenosine production

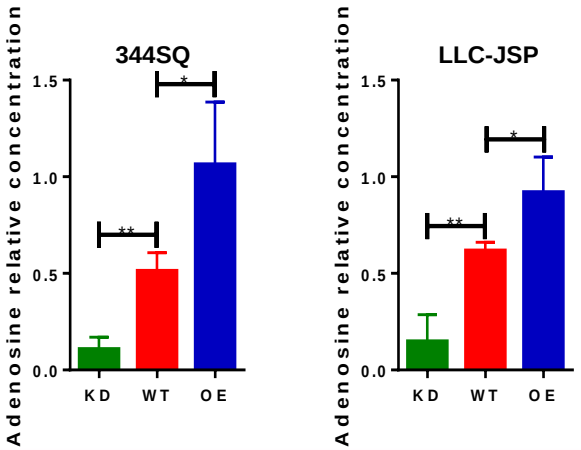


Fradette, 2019.

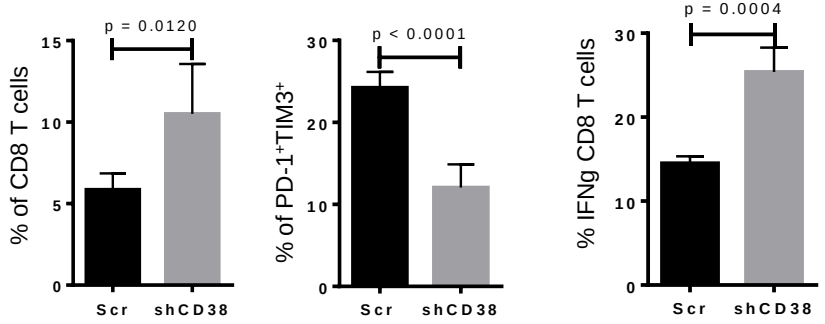
CD38 tumor expression drives growth, metastasis and immune phenotype in KP and LLC models



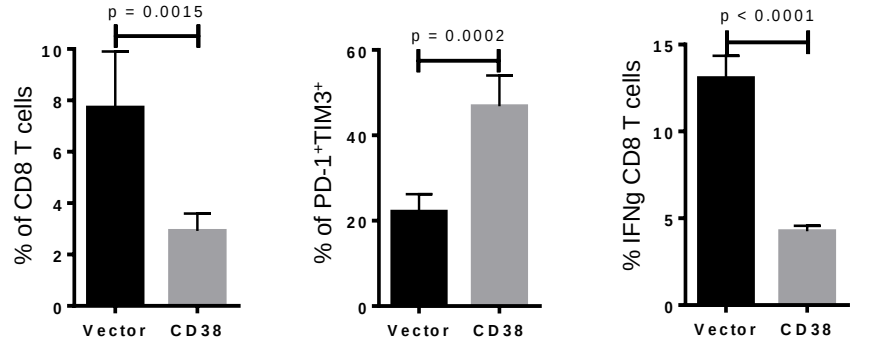
C. Adenosine levels in culture media



D. KP model with CD38 KD

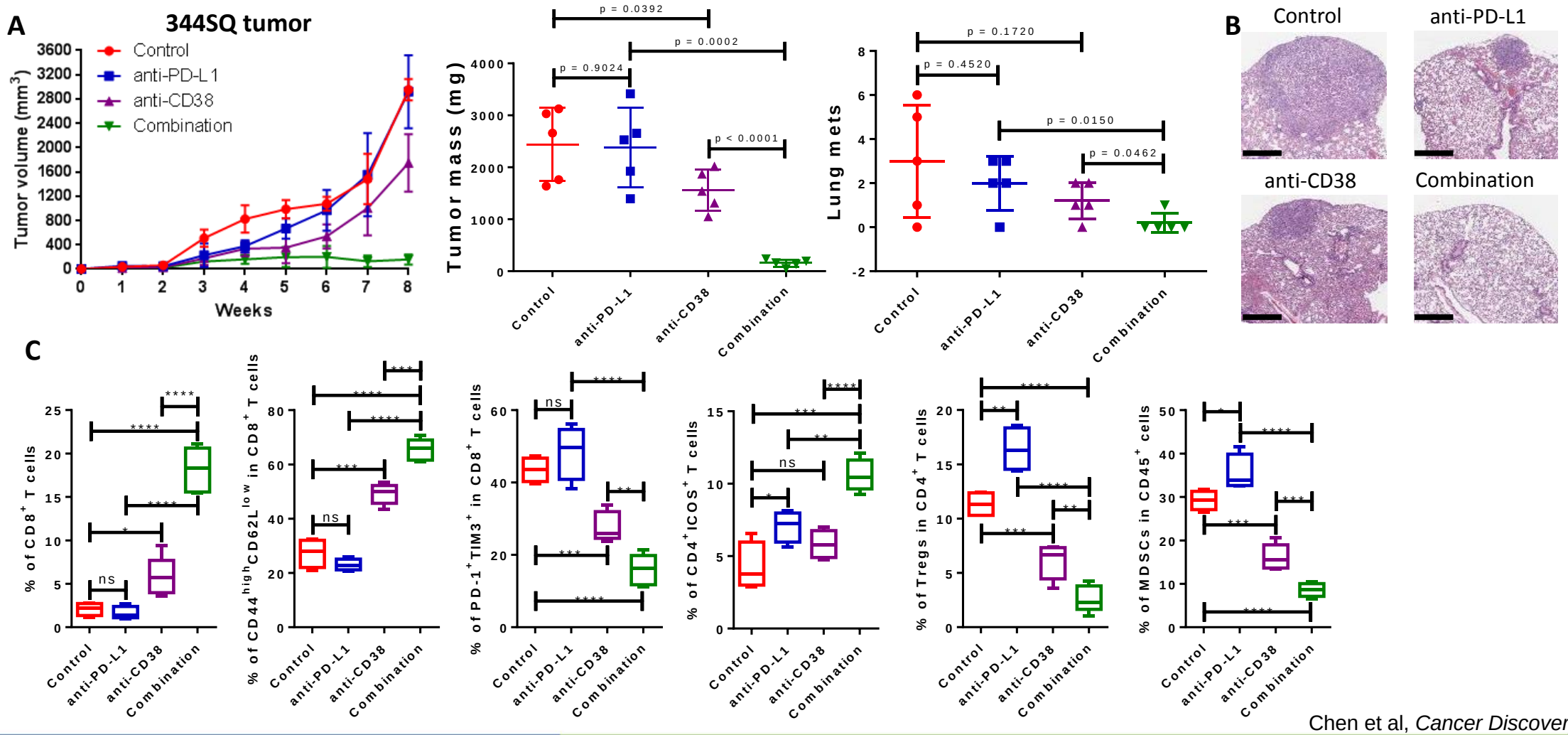


E. KP model expressing CD38



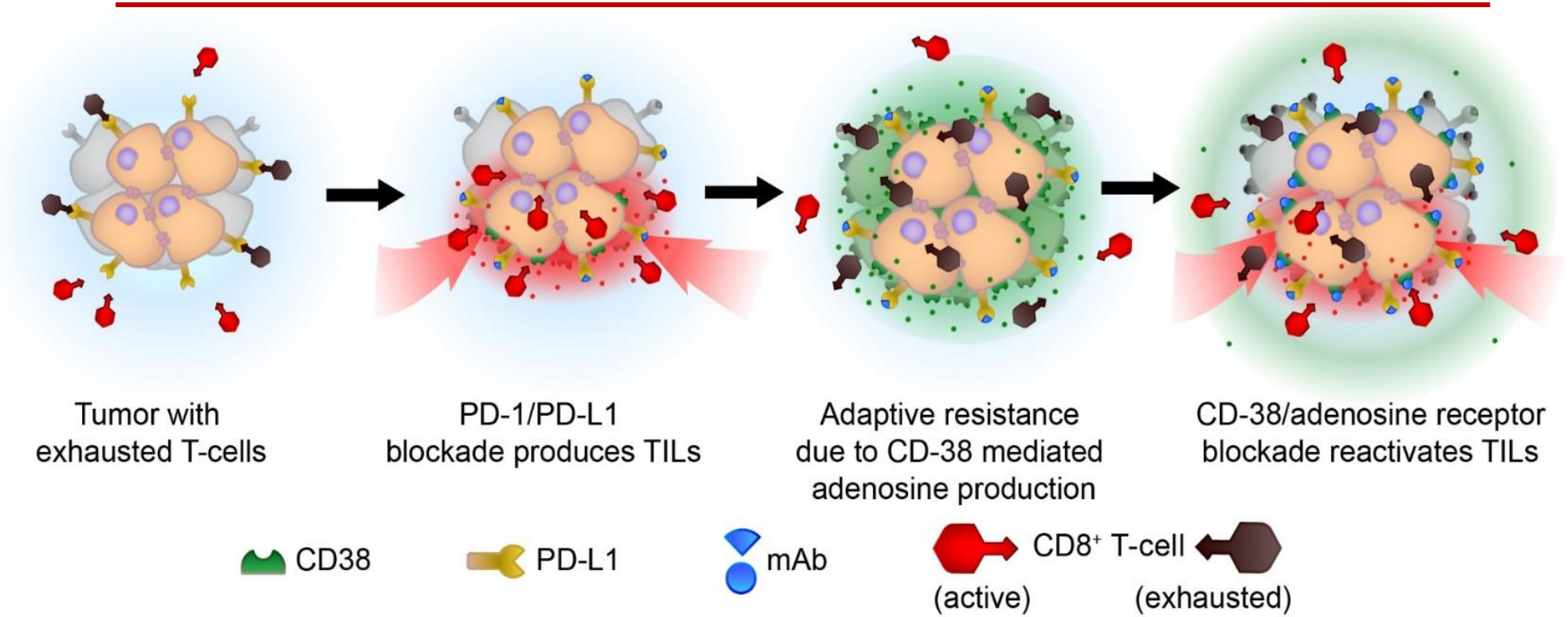
Chen et al, *Cancer Discovery,* 2018.

Combination anti-PD-L1/-CD38 improves therapeutic response in multiple *in vivo* models



Chen et al, *Cancer Discovery*, 2018.

Working Model of Adaptive Immune Suppression

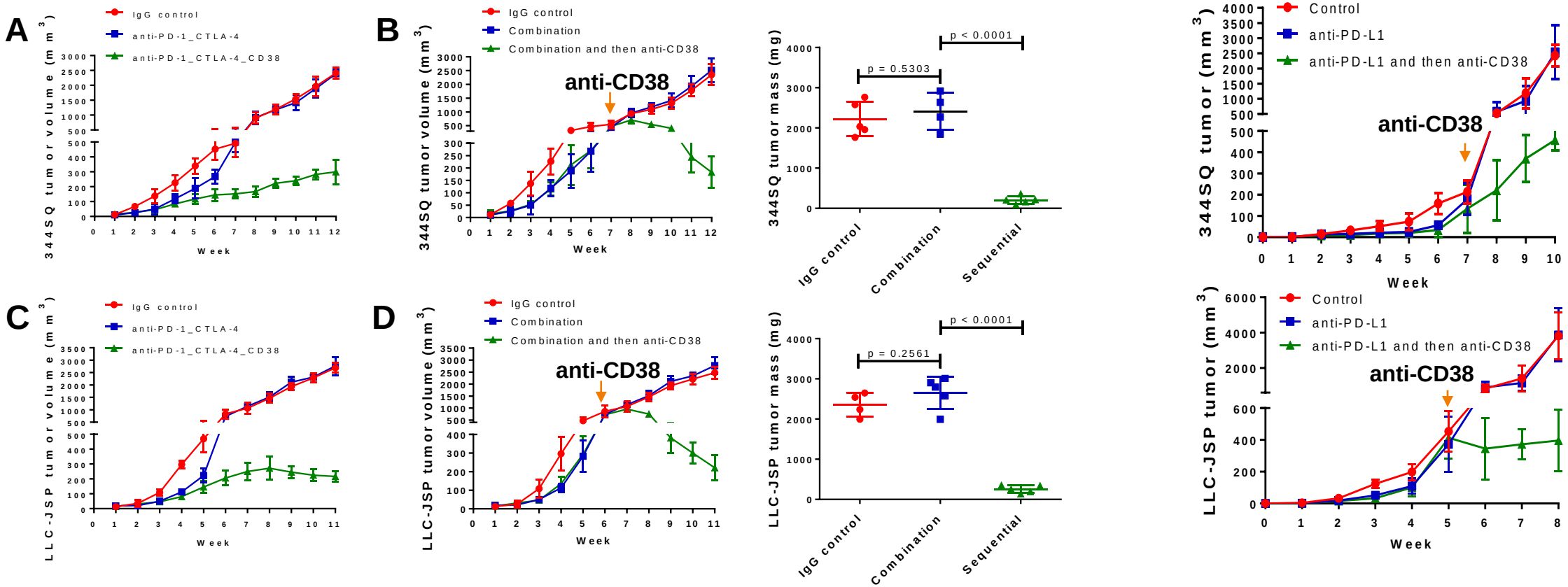


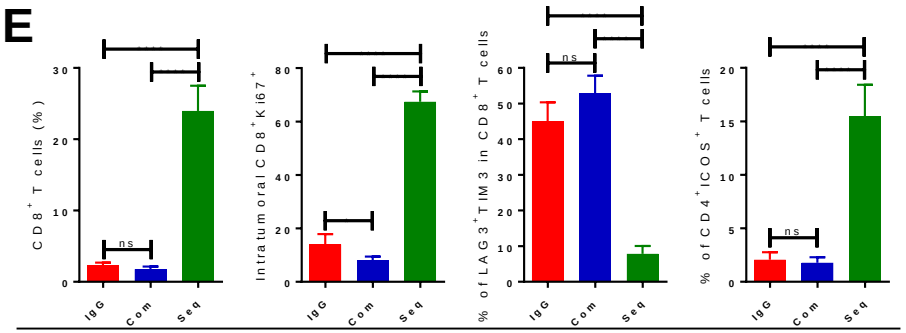
Chen et al, 2018

Open Questions:

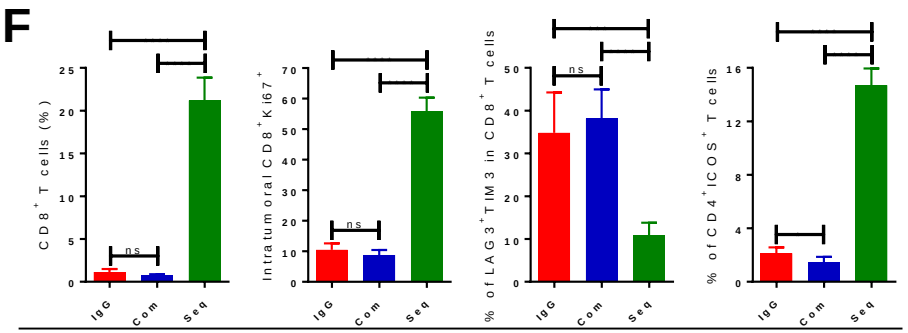
- Does this mechanism apply to any immunotherapy treatment?
- What is the best therapeutic intervention against CD38 or the pathway?
- Besides T cells, are other effector immune cell types important?
- What is/are the best biomarker(s) to select patients and develop these therapies?

Anti-CD38 prevents & reverses the adaptive resistance to PD-1/CTLA-4 blockade





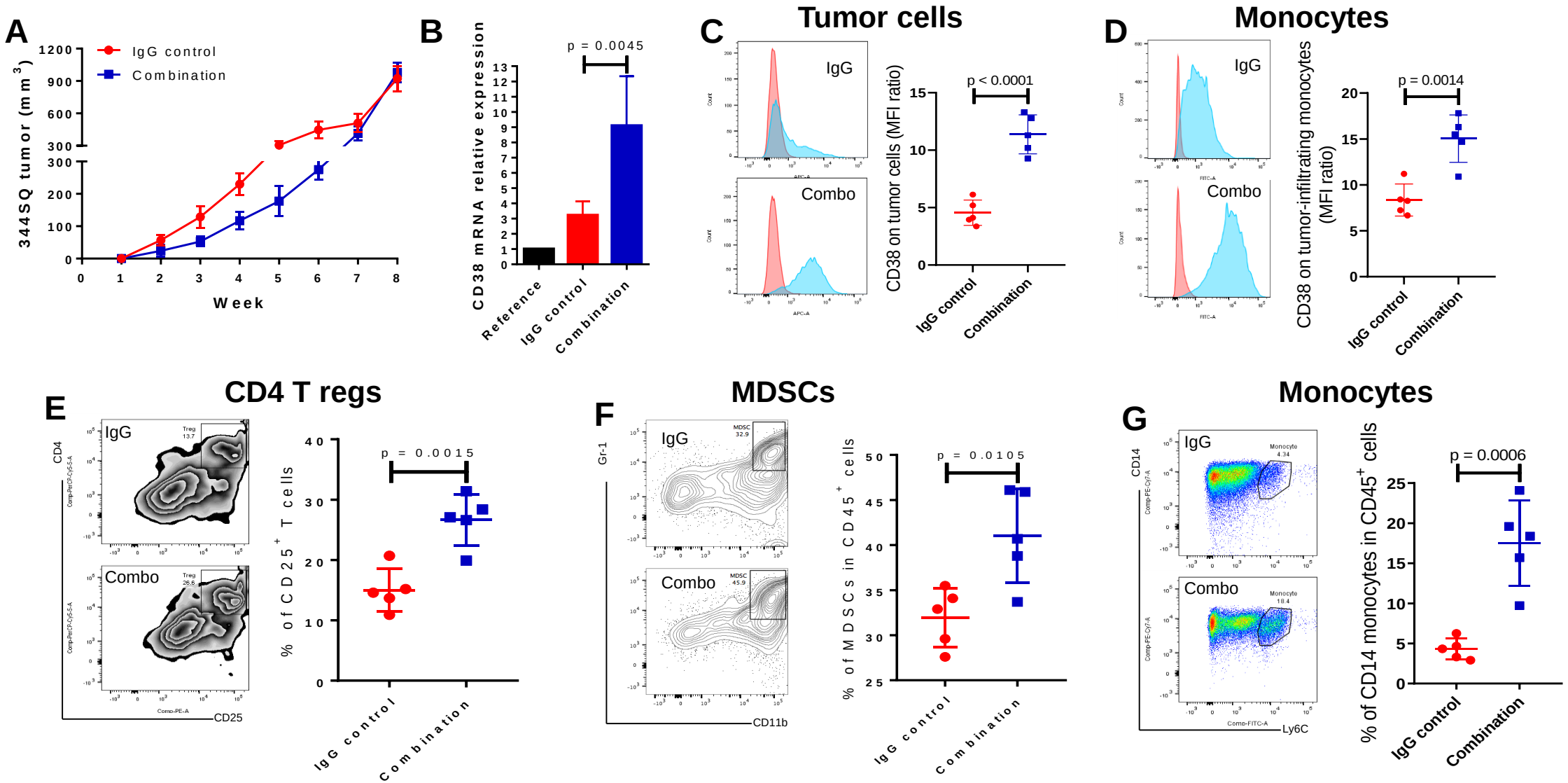
In 344SQ tumors



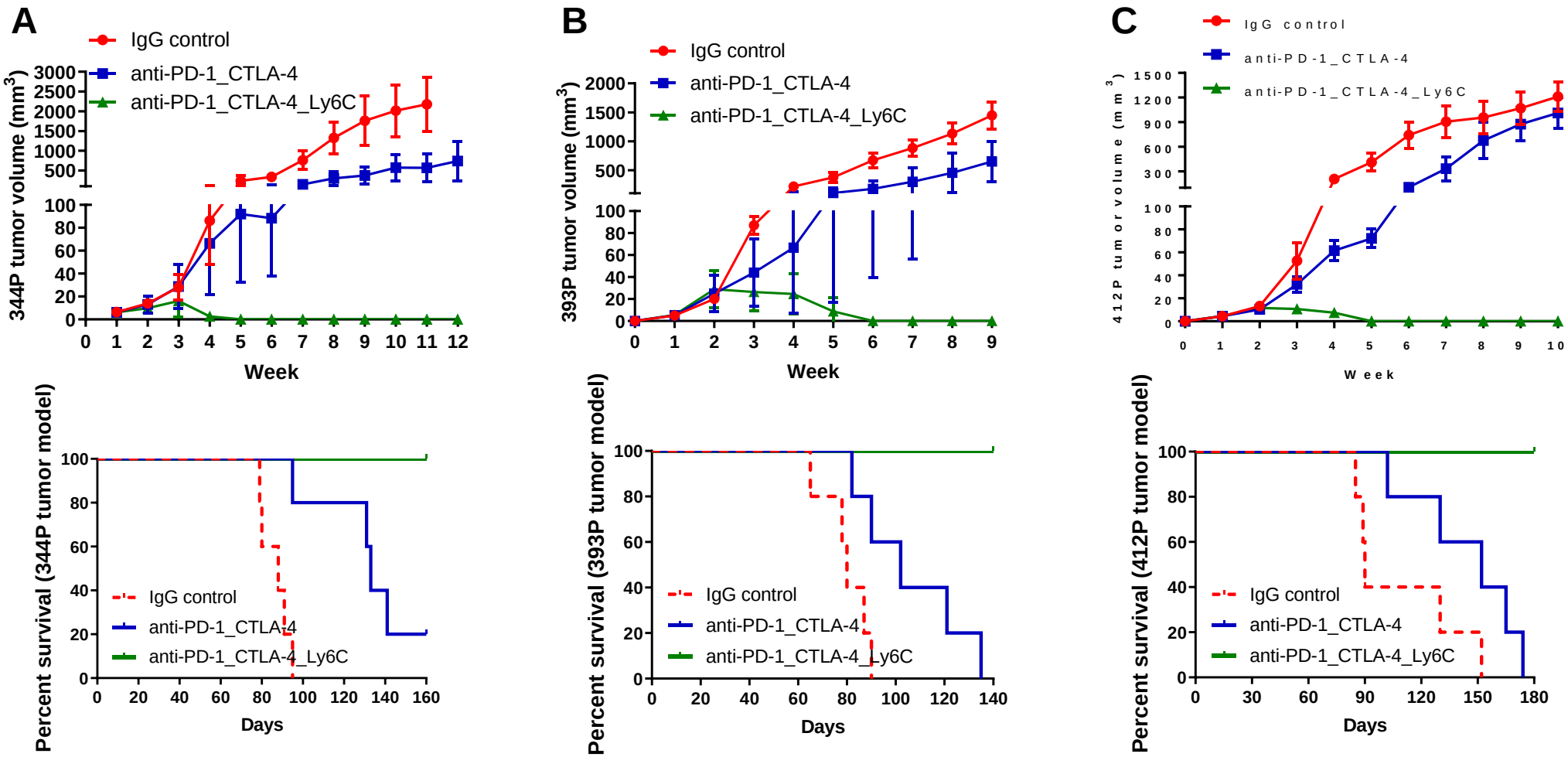
In LLC-JSP tumors

Chen et al, *Unpublished*.

Anti-PD-1/-CTLA-4 resistance is associated with CD38 up-regulation on multiple cell types, including Ly6C$^+$ monocytes

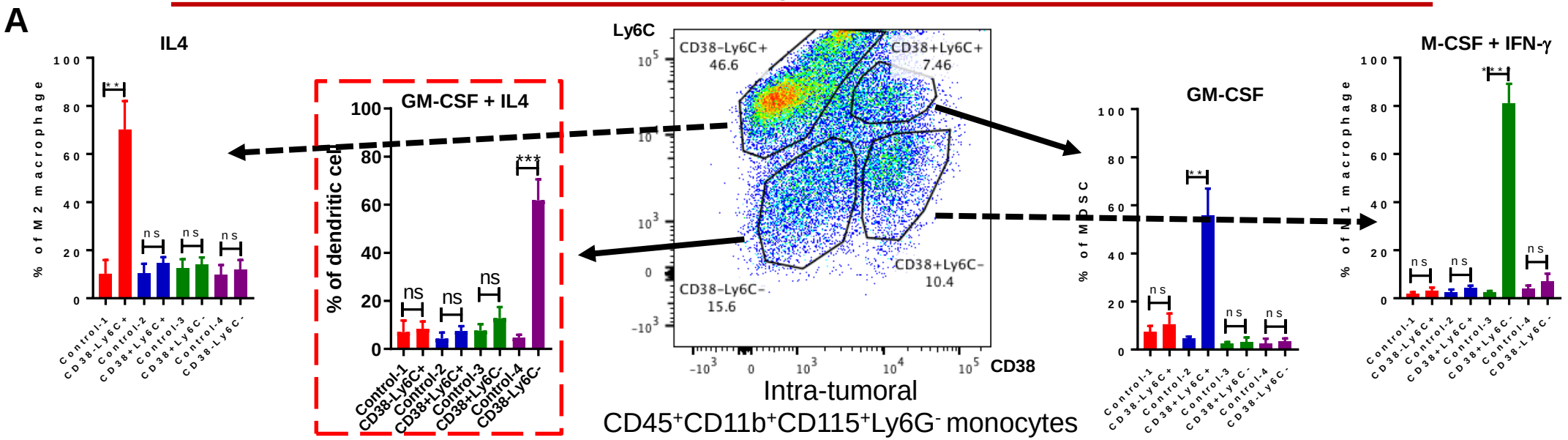


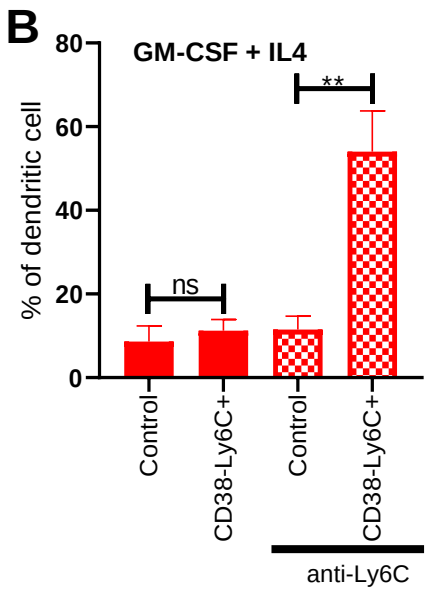
Tumor resistance to anti-PD-1/-CTLA-4 therapy is reversed by Ly6C blockade in multiple models

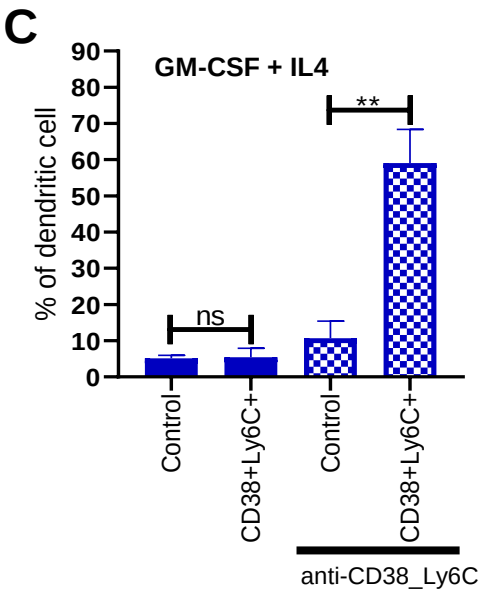


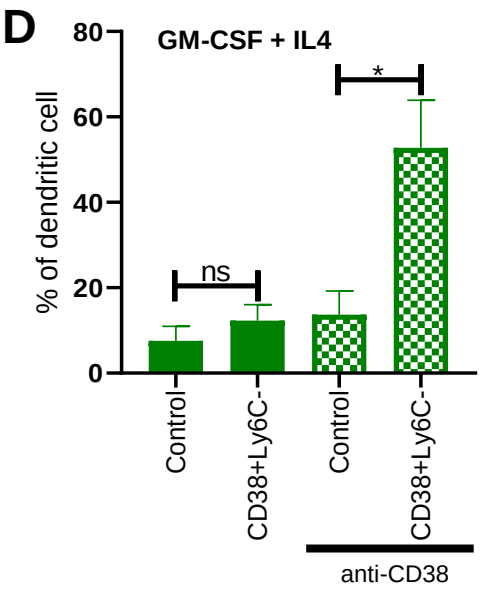
Chen et al, *Unpublished*.

CD38 and Ly6C status define the differentiation potential of intratumoral monocytes into dendritic cells









Dendritic cells present a necessary second signal to cytotoxic CD8 T cells

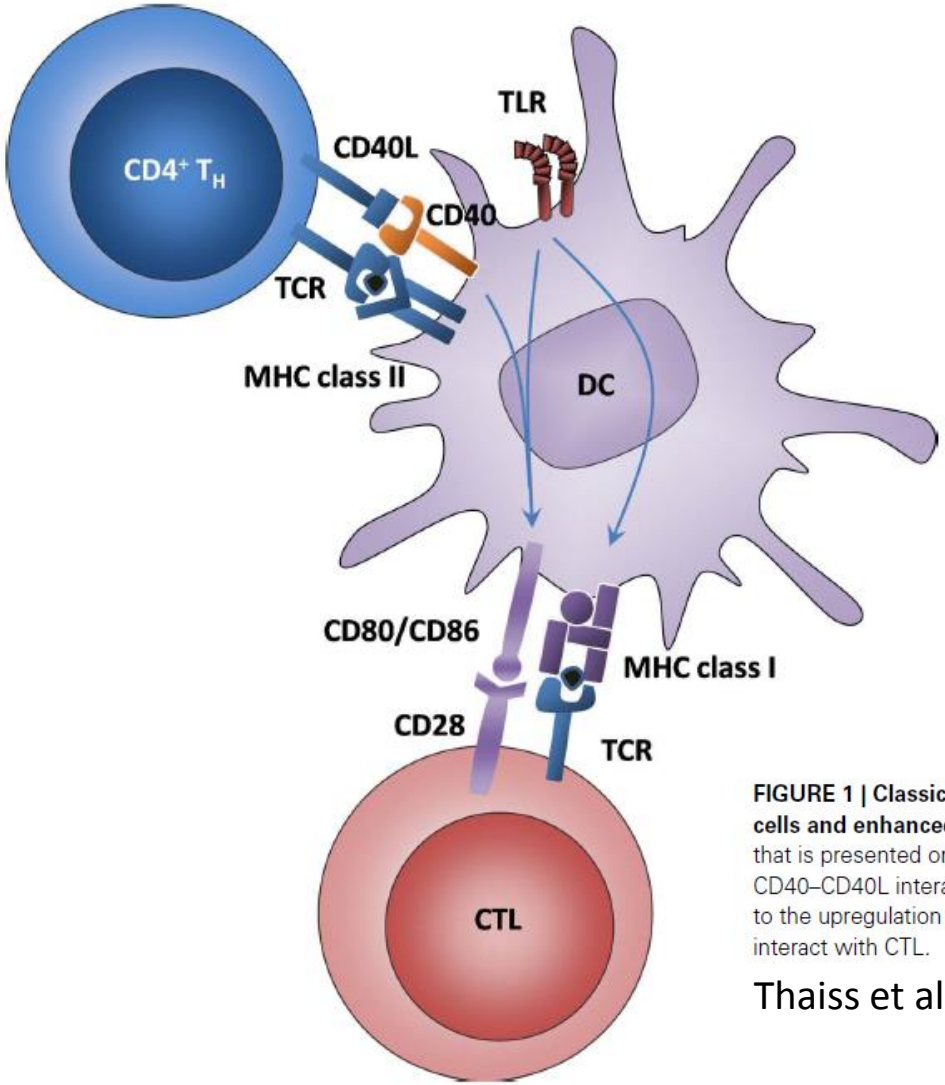
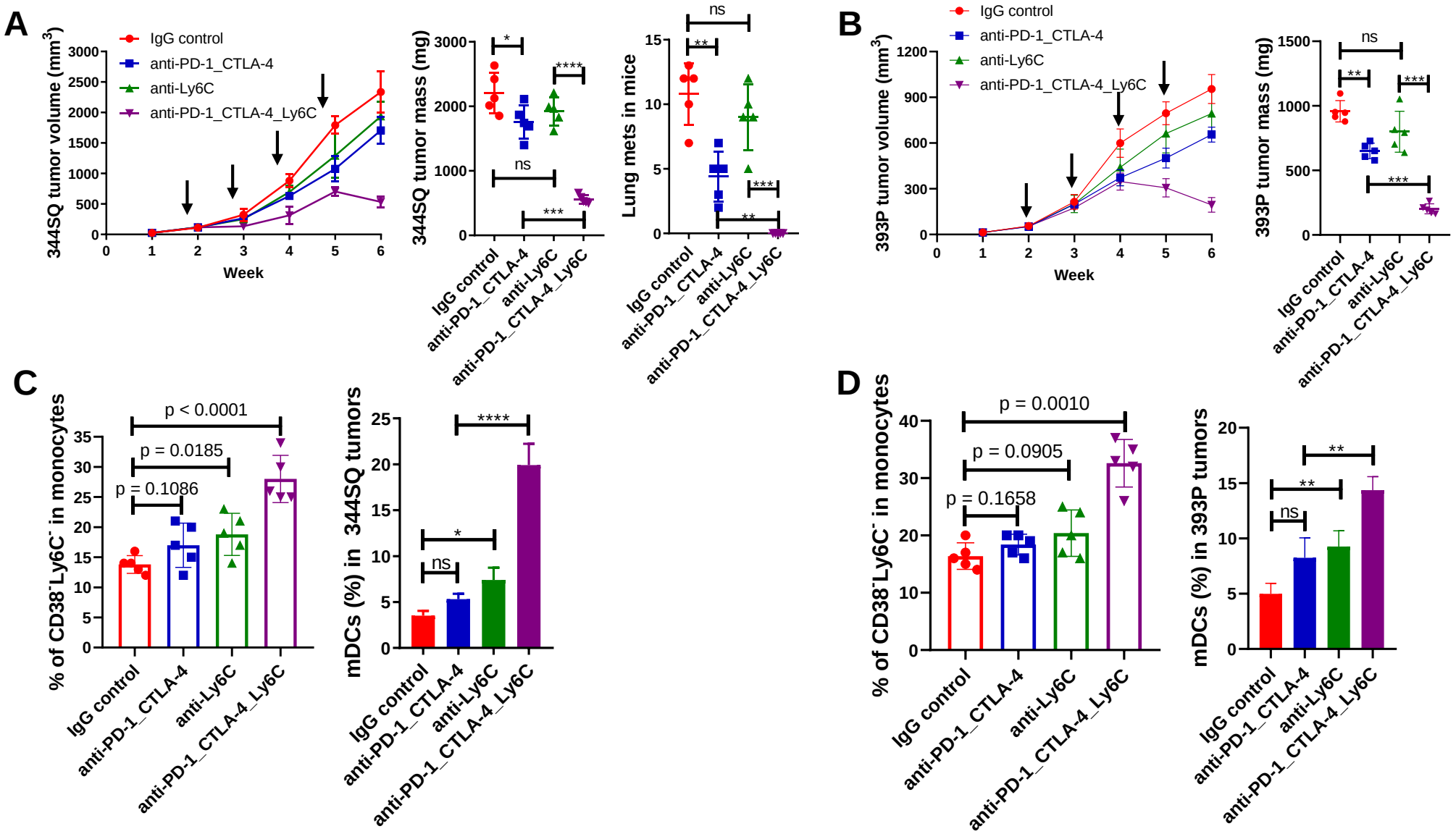


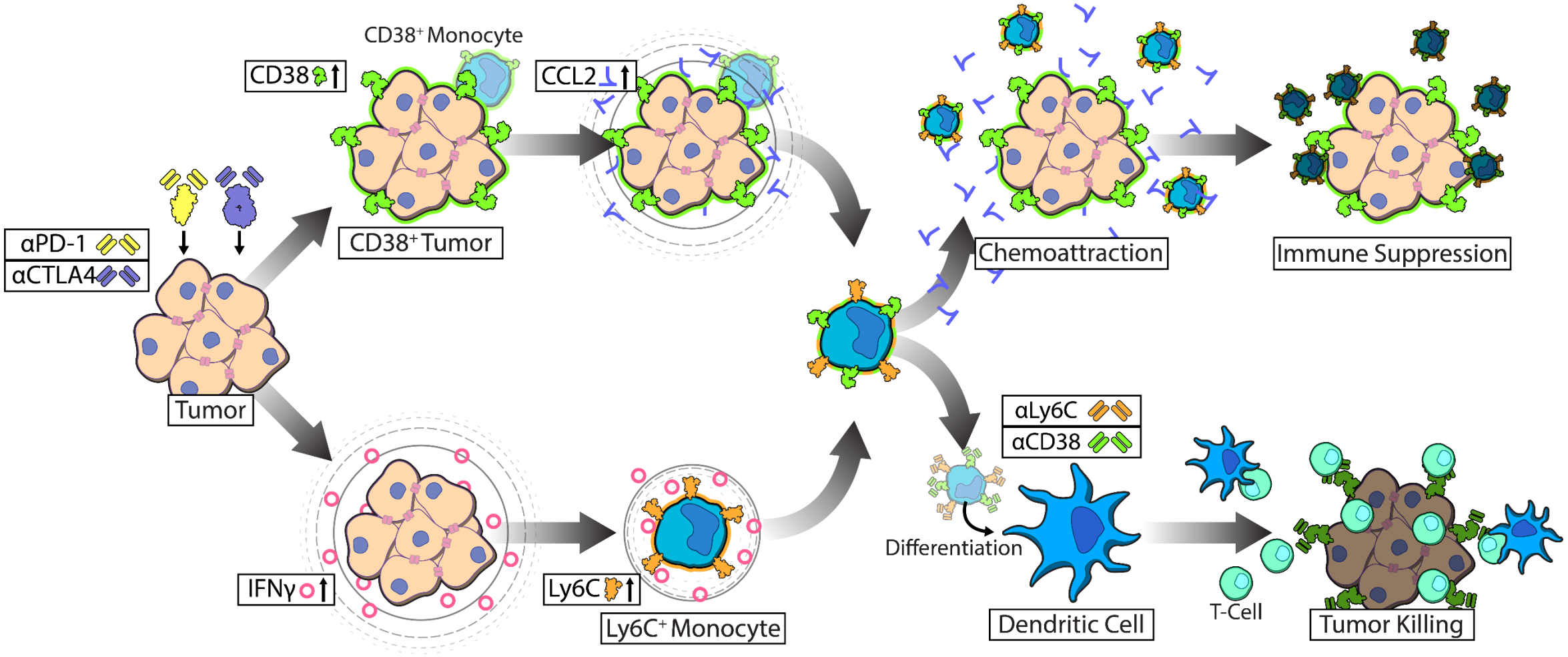
FIGURE 1 | Classical DC licensing for cross-priming is mediated by Th cells and enhanced by TLR ligands. DCs interact with Th cells via antigen that is presented on MHC class II and recognized by the TCR and via CD40–CD40L interactions. The signals downstream of CD40 and TLRs lead to the upregulation of MHC class I and CD80/86, thus allowing the DC to interact with CTL.

Thaiss et al, *Front. in Immunology*, 2011.

CD38^{-}Ly6C^{-} monocytes and mature dendritic cells are enriched in tumors with anti-PD-1/-CTLA-4 /-Ly6C



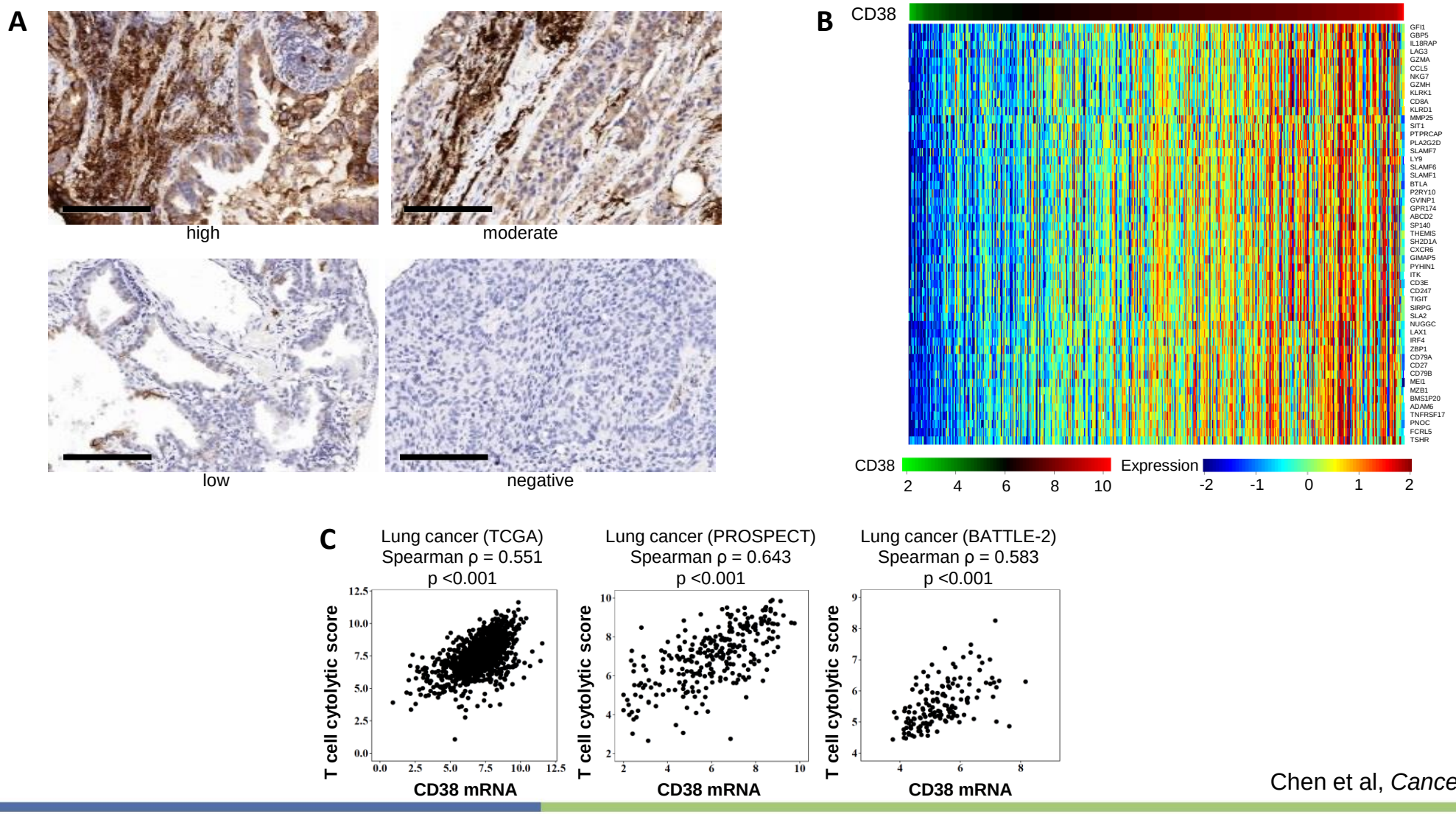
Potential Model of CD38 & Ly6C Effects on Myeloid Subsets and DC maturation



CD38-dependent Ado production also affects CD8 T cell function and DC maturation

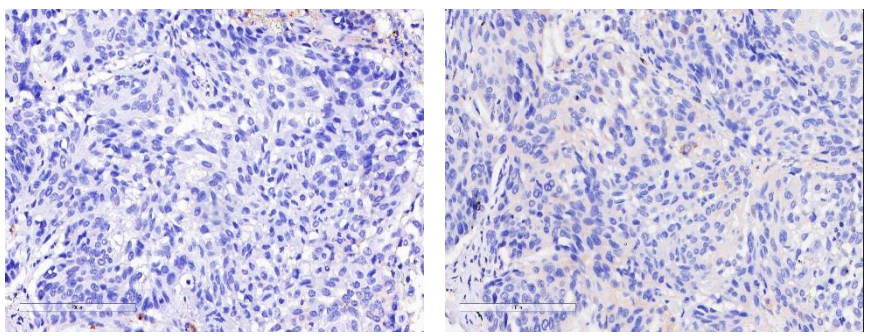
Translational & immune biomarker development in NSCLC

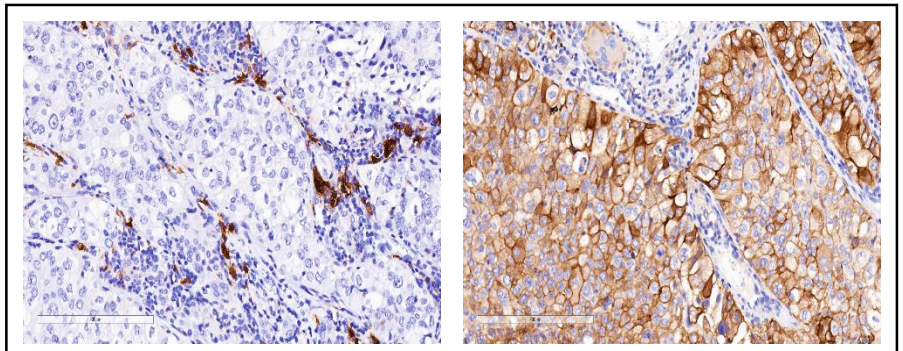
CD38 expression is associated with markers of intratumoral CD8 T cell infiltration

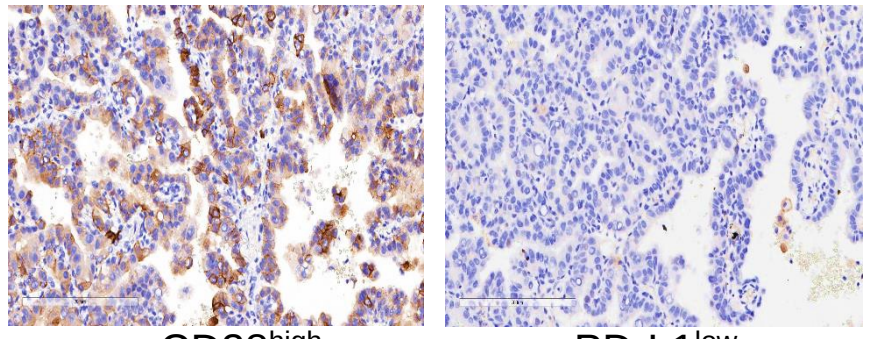


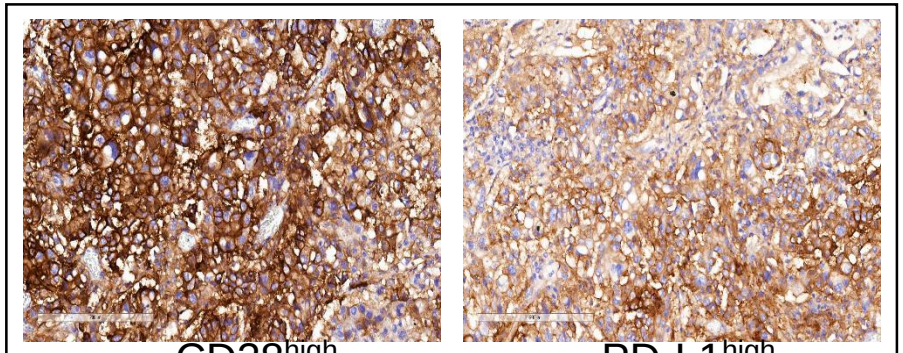
Chen et al, *Cancer Discovery,* 2018.

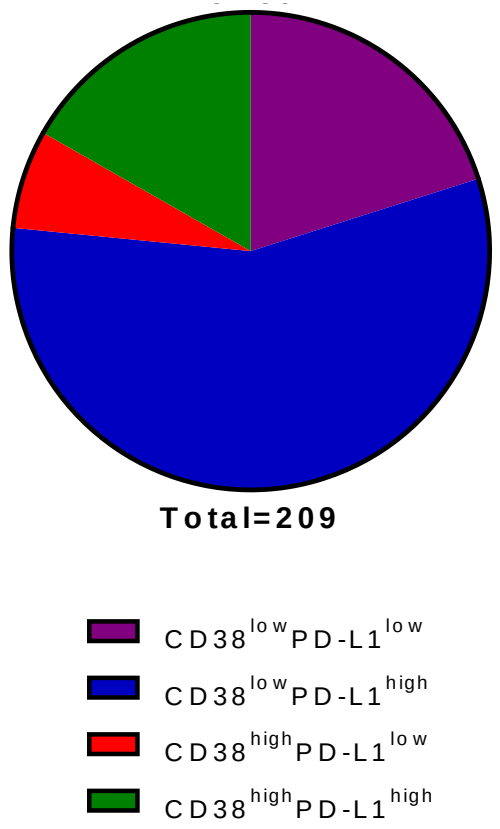
Co-expression of CD38 and PD-L1 in multiple cohorts of treatment-naïve NSCLC tumors





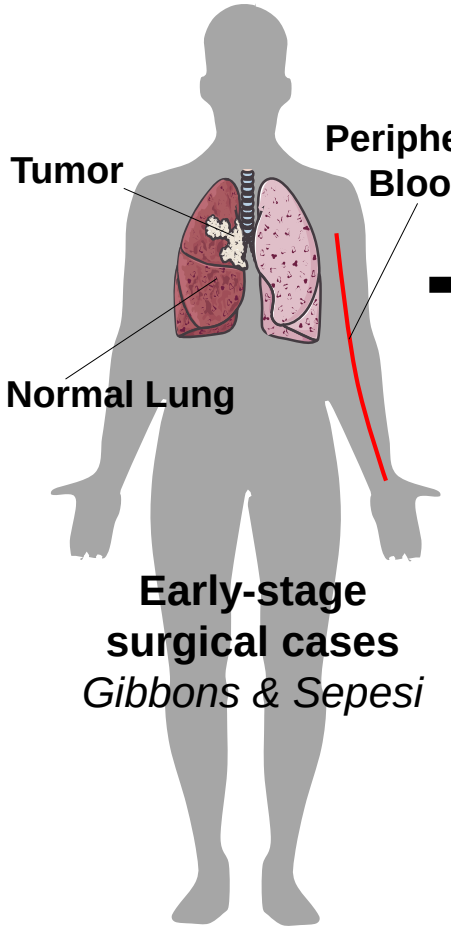






Chen et al, *Cancer Discovery,* 2018.

ICON Project (**I**mmunogenomi**C** pr**O**filing of **N**SCLC)



Early-stage surgical cases
Gibbons & Sepesi

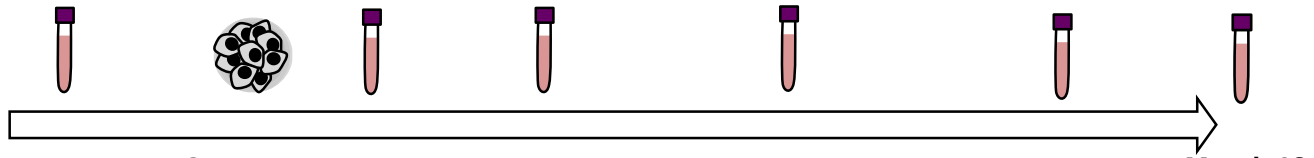
Collection of Tissue & Blood Samples for Profiling

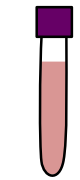
April 28, 2016 – present

- **201** patients consented
- **150** surgical cases - blood & tissue samples collected
- **Longitudinal** blood samples collected post-surgery

Goals:

- Characterize immuno-genomic diversity in early-stage NSCLC.
- Establish biomarkers for translation into clinical practice.
- Build infrastructure for biomarker-driven early-stage clinical trials with IO agents.





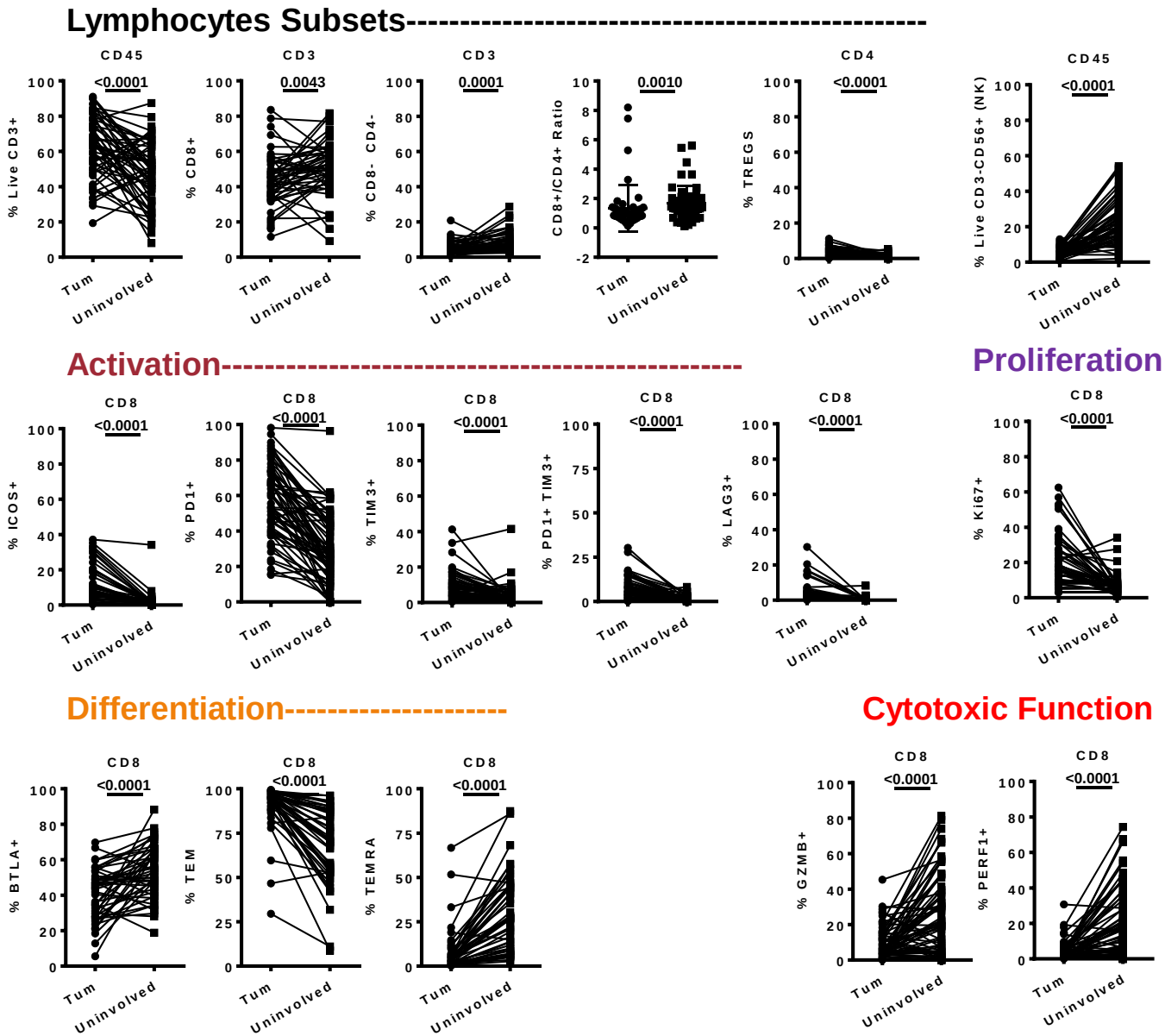
Blood

Circulating tumor DNA
Plasma analysis
T cell repertoire

Tumor

Whole exome sequencing
Neoantigen prediction
RNA sequencing
Reverse phase protein array
Flow cytometry
Cytometry by Time-of-Flight
Multiplex immunofluorescence
T cell repertoire
Tumor-infiltrating lymphocyte expansion

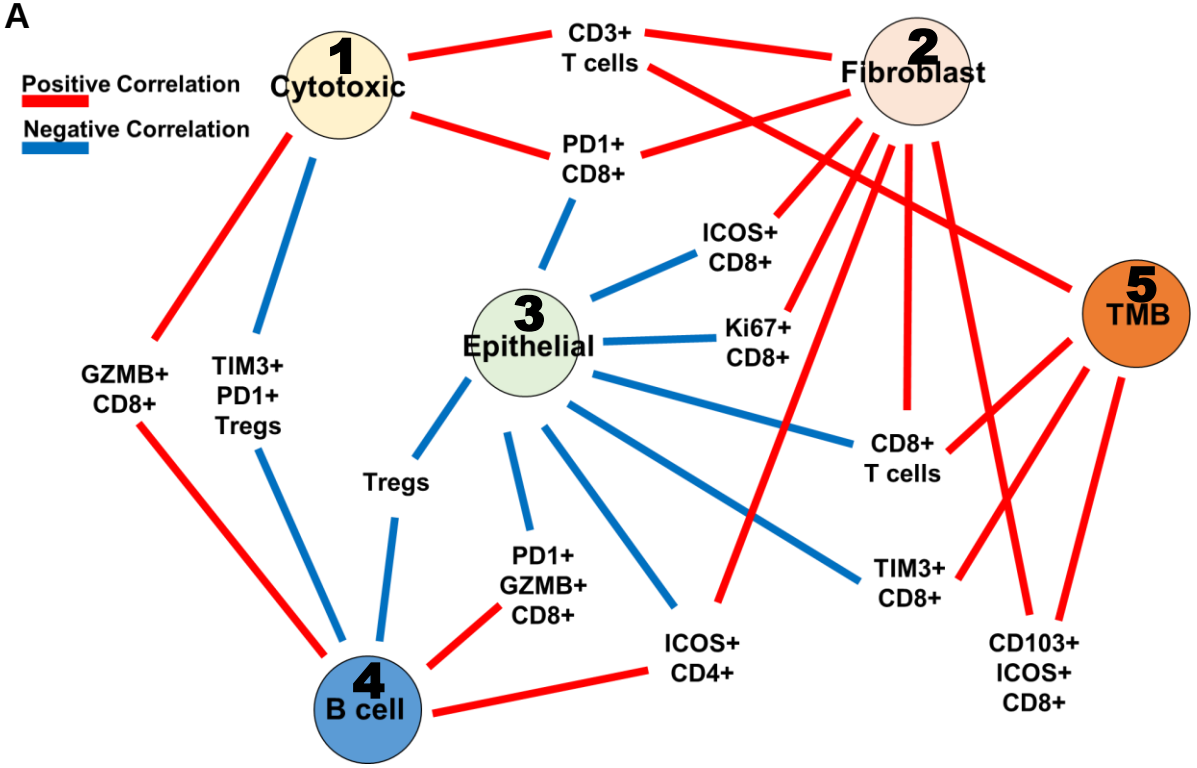
T cell profiles from multi-parameter flow for fresh tumor vs matched normal lung



Federico, Bernatchez, MDACC

Mapping tumor subsets by correlation of T cell profiles with tumor RNA signatures

A

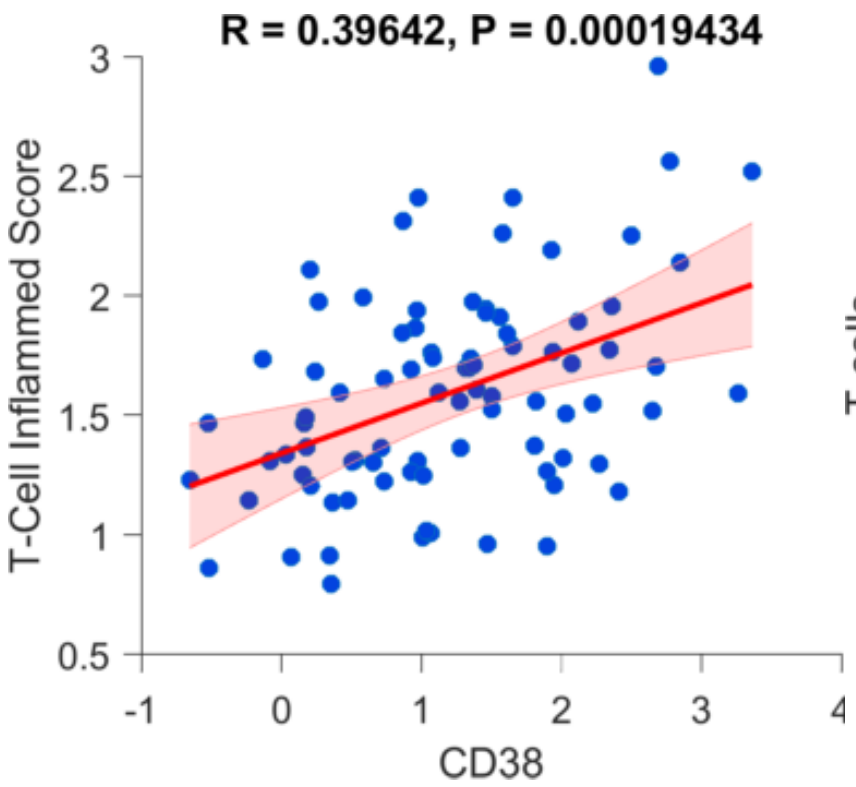


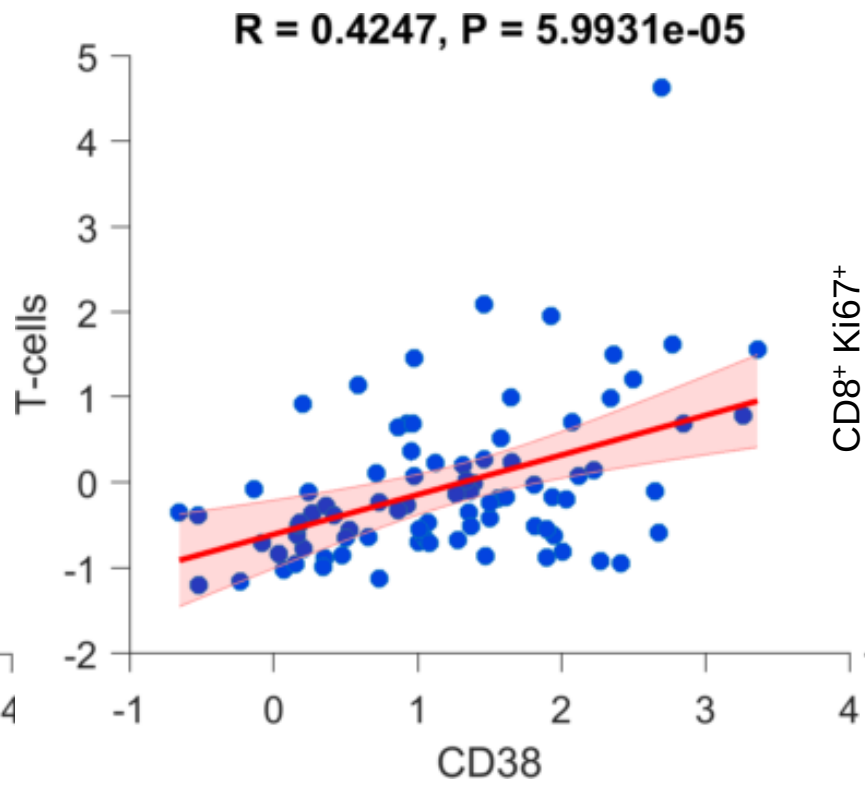
B

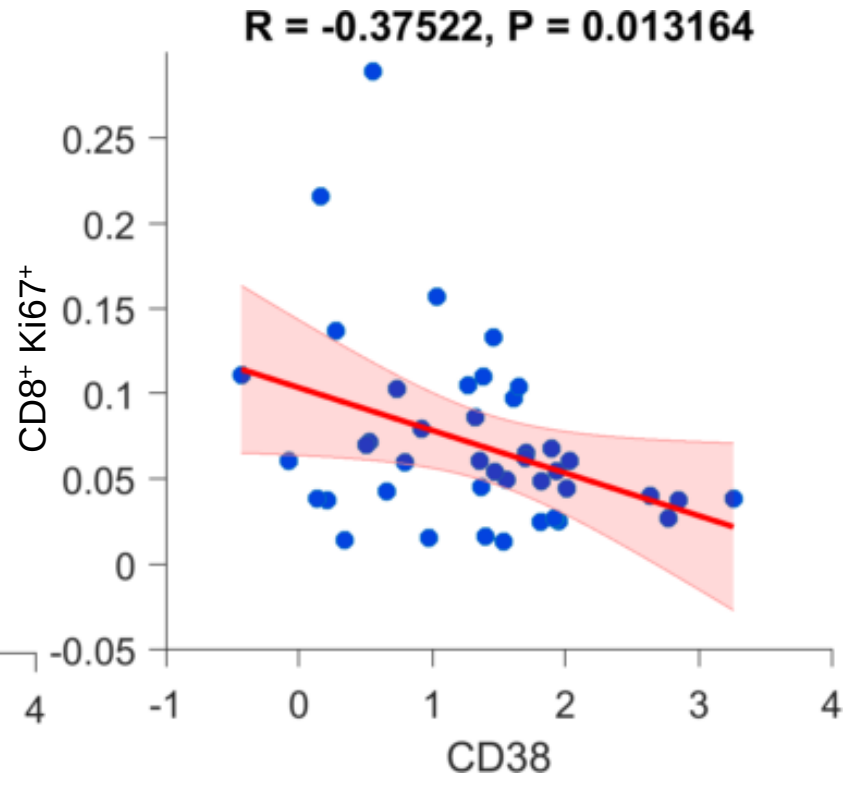
	RNA Signature				
	Cytotoxic	B Cells	Epithelial	Fibroblast	TMB
GzmB$^+$ CD8$^+$	■	■			
TIM3$^+$ PD1$^+$ Tregs	■	■			
TIM3$^+$ PD1$^-$ Tregs	■	■	■		
Tregs		■	■		
PD1$^+$ GzmB$^+$ CD8$^+$		■	■		
CD3$^+$	■			■	■
ICOS$^+$ CD103$^+$ CD8$^+$				■	■
CD8$^+$			■	■	■
ICOS$^+$ CD4$^+$		■	■	■	
ICOS$^+$ CD8$^+$			■	■	
Ki67$^+$ CD8$^+$			■	■	
PD1$^+$ CD8$^+$	■		■	■	
TIM3$^+$ CD8$^+$			■		■

Federico, Karpinets, McGrail, MDACC

CD38 levels correlate with T Cell inflamed score, T cell infiltrate and suppression of CD8 proliferation in the ICON samples

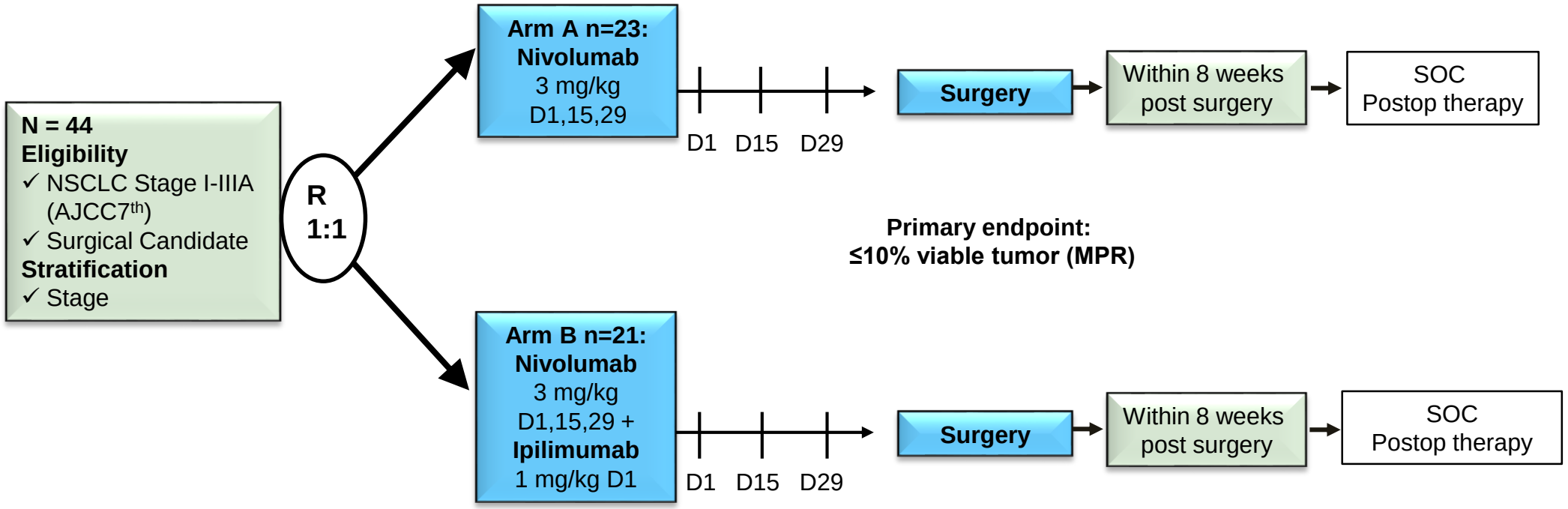






Federico, McGrail, MDACC

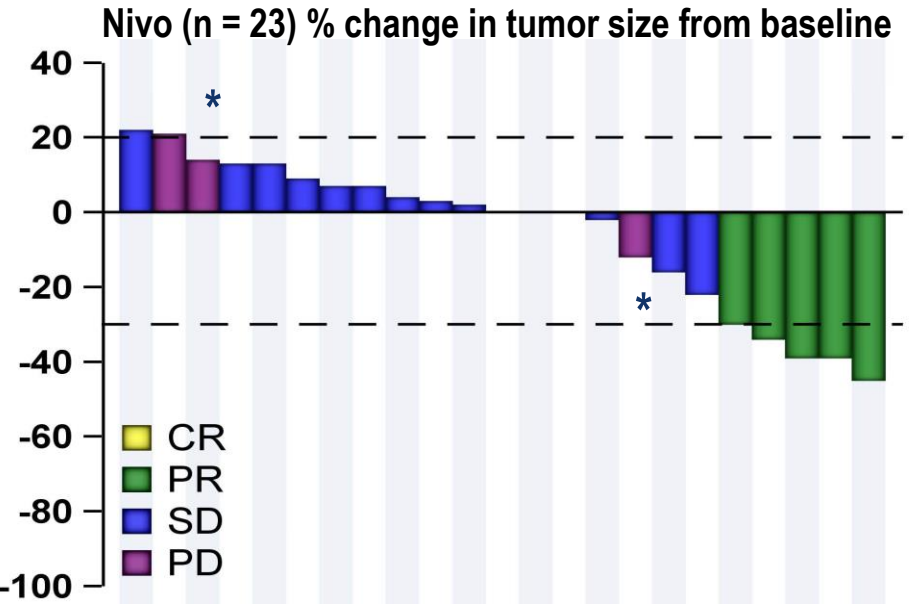
NEOSTAR: phase II study of i**n**duction ch**e**ckpoint bl**o**ckade for untreated **st**age I-IIIA NSCLC **a**menable for surgical **r**esection

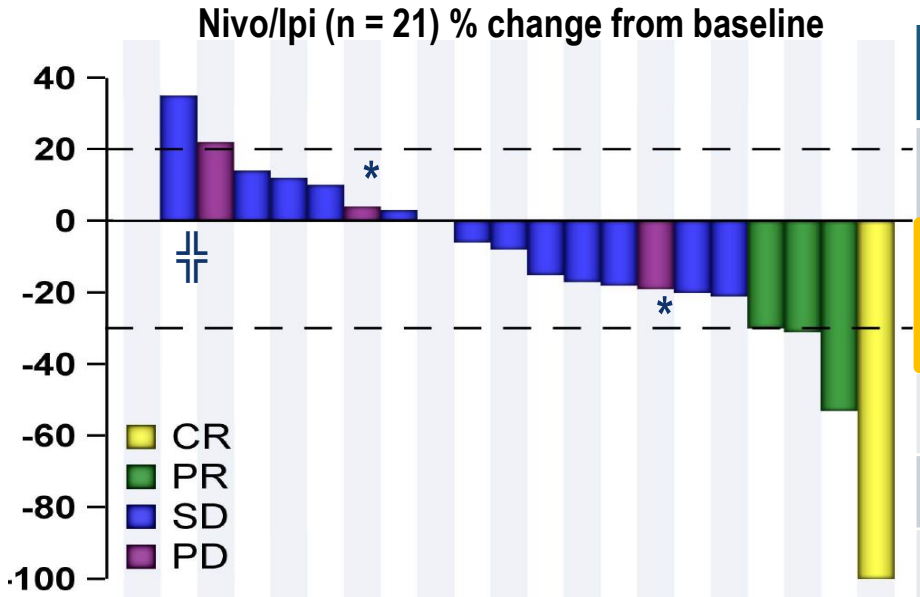


Successful enrollment of arms A and B completed in 17 months

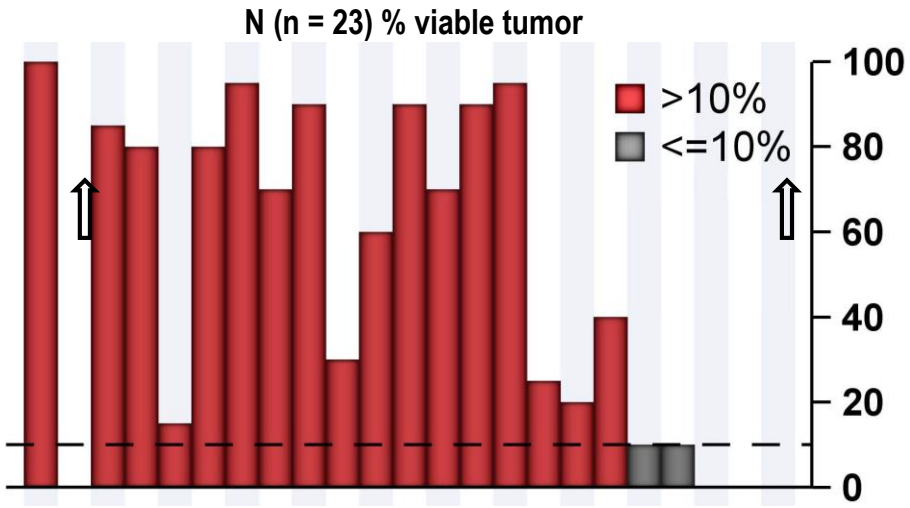
PI: T Cascone
Co-PI: B. Sepesi

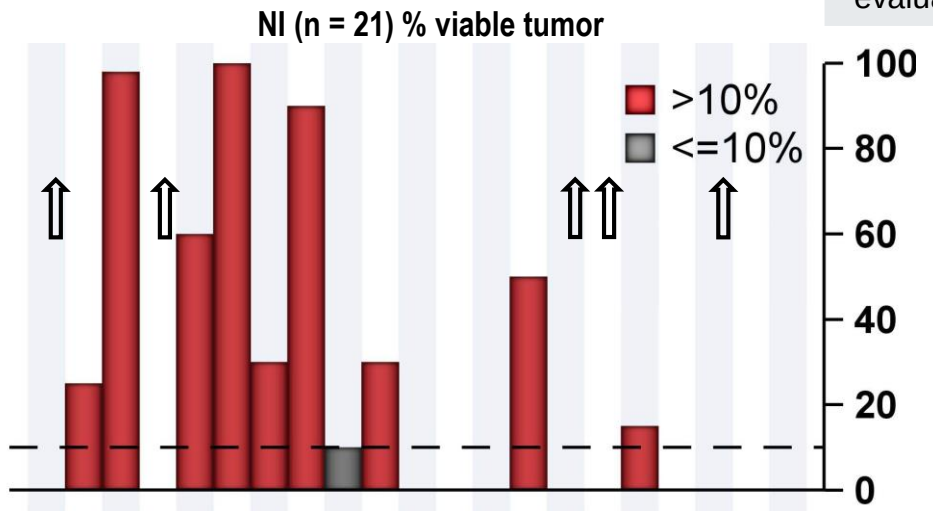
RECIST Responses are positively associated with MPR





Response (RECIST)	Overall n = 44	N n = 23	NI n = 21
	n (%)	n (%)	n (%)
CR	**1 (2%)**	**0 (0%)**	**1 (5%)**
PR	**8 (18%)**	**5 (22%)**	**3 (14%)**
SD	28 (64%)	15 (65%)	13 (62%)
PD	6 (14%)	3 (13%)	3 (14%)
Not evaluable	1 (2%)	0 (0%)	1 (5%)#





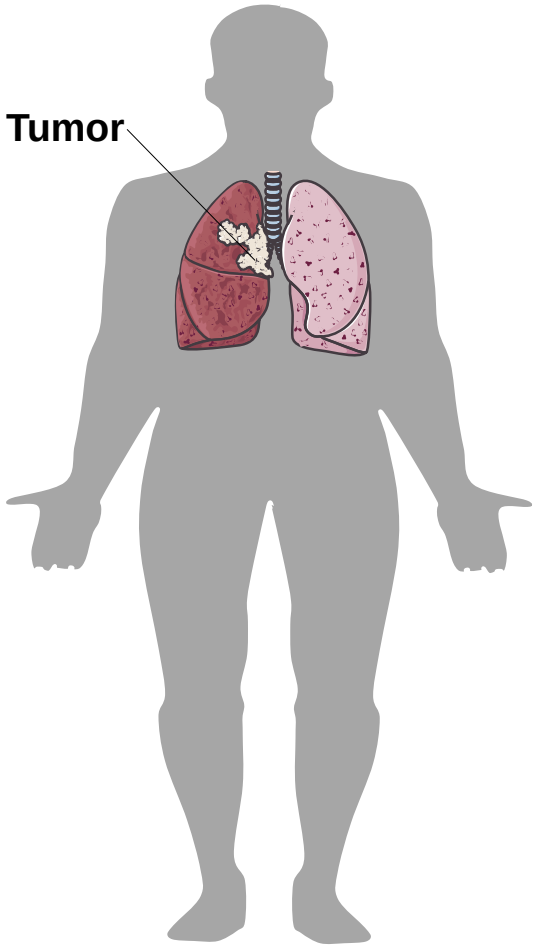
⇧ no surgery on trial (5 no surgery, 2 surgeries off trial)

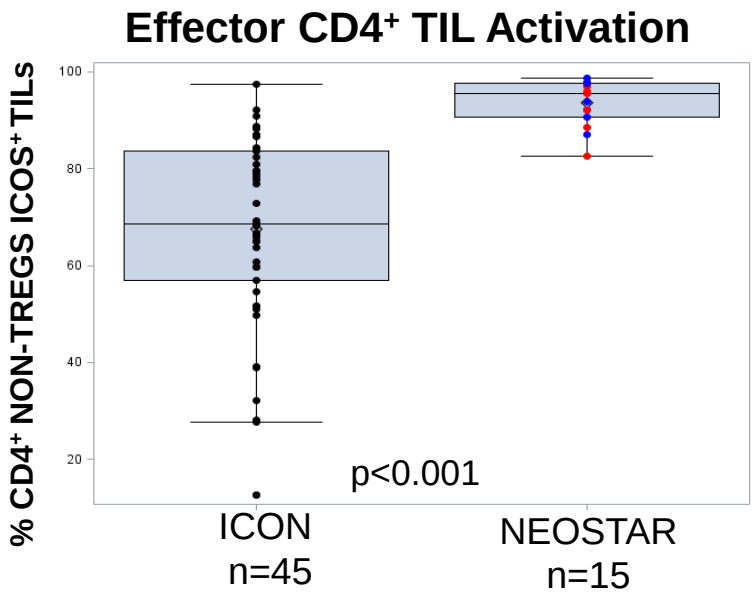
* Overall PD due to new lesions; ╬ SD with cavitation, wall thickness increase/inflammation

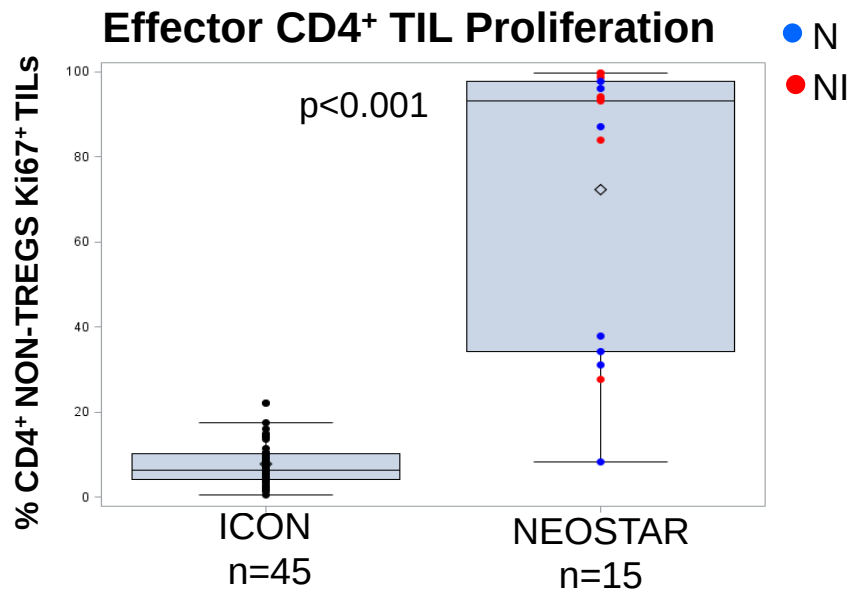
Cascone T, ASCO 2019 Abstract 8504.

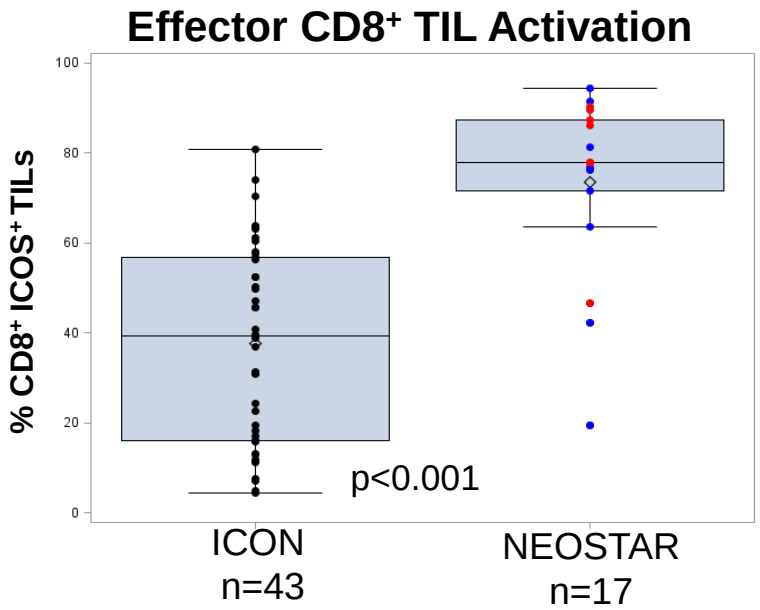
Neoadjuvant N and NI increase proliferative/activated TILs vs. untreated lung tumors (ICON set)

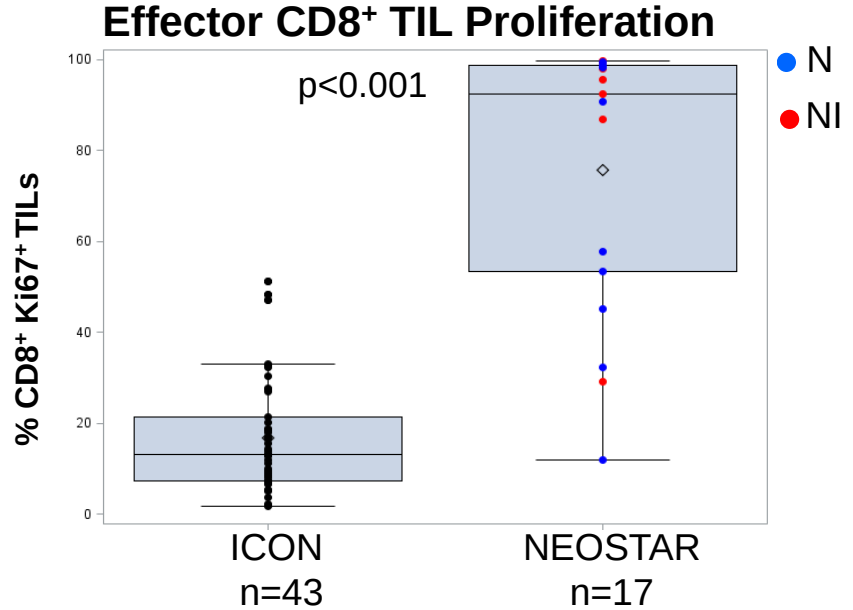
ICON (**I**mmunogenomi**c** Profiling **o**f **N**SCLC)
Stage IB-IIIA resected tumors











Cascone ESMO Annual Meeting 2018, LBA_49.

Take home messages

- Multiple mechanisms of acquired resistance to PD-(L)1 and CTLA-4 blockade are activated upon an enhanced intratumoral immune infiltration.
- CD38 alters the tumor metabolic microenvironment & affects multiple immune cell types.
- Study of pre-clinical models allows us to address MOA, test causation and assess treatment strategies for IO agents in NSCLC.
- Parallel analysis of patient specimens will best guide our understanding of the broader immune landscape, development of clinical biomarkers and testing for treatment strategies.

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